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## Optimisation of neonatal ventilation from birth using physiological measurements as outcomes

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**Optimisation of neonatal ventilation from birth  
using physiological measurements  
as outcomes**

**Thesis submitted for the degree of  
MD (Res)**

**King's College London  
University of London**

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Professor Anne Greenough**

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# Abstract

**Aim:** To optimize mechanical ventilation in the labour suite and on the neonatal unit using the results of physiological measurements as outcomes. A series of studies was undertaken to test the following hypotheses.

1. During the resuscitation of prematurely born infants, inflation pressures of 25/5 cmH<sub>2</sub>O would increase the expired tidal volume and end tidal carbon dioxide levels. In addition, maintenance of the first five inflations for two to three seconds would lead to higher tidal volumes.
2. In infants born at or near term, volume targeted ventilation (VTV) when compared to pressure limited ventilation (PLV) would be associated with shorter time to extubation, reduced work of breathing and better respiratory muscle strength.
3. In a dynamic lung model representing bronchopulmonary dysplasia, resistive unloading during proportional assist ventilation (PAV) would reduce the inspiratory load.
4. In infants with evolving bronchopulmonary dysplasia, PAV when compared to assist control ventilation (ACV) would be associated with reduced work of breathing, increased respiratory muscle strength and be associated with less ventilator-infant asynchrony and improved oxygenation as indicated by the oxygenation index (OI).
5. Extubation failure would be predicted by the tension time index of diaphragm (TTdi) and the tension time index of respiratory muscles (TTmus).

## Results:

1. The resuscitation study demonstrated that higher inflation pressures, but not longer inflation times produced significantly higher expired tidal volumes.
2. There were no significant differences in the time to successful extubation in at or near term-born infants supported by VTV or PLV; however, VTV was associated with significantly fewer episodes of hypocarbia.
3. The in-vitro study of PAV showed that the resistive unloading was relatively ineffective and hence as currently delivered is unlikely to be of clinical benefit to infants with a high resistance load.
4. PAV compared with ACV in prematurely born infants ventilated beyond the first week after birth resulted in a reduced work of breathing and a lower OI.
5. The TTdi study demonstrated that the TTdi and TTmus results significantly differed according to extubation outcome in ventilated infants. Overall TTdi  $\geq 0.08$  had 83% sensitivity and 81% specificity (90% sensitivity and 60% specificity in the preterm infants) in predicting extubation failure. Overall TTmus  $\geq 0.19$  had 50% sensitivity and 100% specificity (54% sensitivity and 100% specificity in the preterm infants) in predicting extubation failure.

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## Abbreviations used in this thesis

ACV	Assist/Control Ventilation
ARDS	Adult Respiratory Distress Syndrome
BAL	Bronchoalveolar Lavage
BAPM	British Association of Perinatal Medicine
BLISS	Baby Life Support Systems
BPD	Bronchopulmonary Dysplasia
CDH	Congenital Diaphragmatic Hernia
CI	Confidence Interval
Cm	centimeters
CMACE	Centre for Maternal and Child Enquiries
CMV	Continuous Mandatory Ventilation
CPAP	Continuous Positive Airway Pressure
CMV	Conventional Mechanical Ventilation
ECMO	Extracorporeal Membrane Oxygenation
Edi	Electrical activity of the diaphragm
EIT	Electrical Impedance Tomography
ETT	Endotracheal Tube
FEV1	Forced expiratory volume in 1 second
FiO <sub>2</sub>	Fraction of inspired oxygen
gm	gram
GI	Gastrointestinal
H <sub>2</sub> O	Water
HFOV	High Frequency Oscillatory Ventilation
HIE	Hypoxic Ischaemic Encephalopathy
hr	hour(s)
Hz	Hertz
IL-8	Interleukin 8
IMV	Intermittent Mandatory Ventilation
IPPV	Intermittent Positive Pressure Ventilation
IVH	Intraventricular Haemorrhage

Kg	kilogram
kPa	kilopascal
L	Litre
LNU	Local Neonatal Unit
MAP	Mean Airway Pressure
MAS	Meconium Aspiration Syndrome
MD	Mean Difference
min	minute
MIP-2	Macrophage Inflammatory Protein 2
ml	milliliters
NAVA	Neurally Adjusted Ventilatory Assist
NHS	National Health Service
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NO	Nitric oxide
PaCO <sub>2</sub>	Partial pressure of carbon dioxide in arterial blood
PaO <sub>2</sub>	Partial pressure of oxygen in arterial blood
PAV	Proportional Assist Ventilation
Paw	Airway pressure
PDA	Patent Ductus Arteriosus
Pdi	Transdiaphragmatic pressure
PEEP	Positive End-Expiratory Pressure
Pemax	maximal expiratory pressure
Pgas	Gastric pressure
pH	power of hydrogen
PICU	Paediatric Intensive Care Unit
Pimax	maximal inspiratory pressure
PIP	Peak Inflation Pressure
PLV	Pressure-limited ventilation
PMA	Postmenstrual age
Poes	Oesophageal pressure
P <sub>0.1</sub>	respiratory drive
PPHN	Persistent Pulmonary Hypertension

	of the Newborn
Ppl	Pleural pressure
ppm	parts per million
PRVC	Pressure-Regulated Volume Control
PSV	Pressure Support Ventilation
PPV	Positive Pressure Ventilation
PTPdi	Transdiaphragmatic Pressure-Time Product
PVL	Periventricular leukomalacia
RCT	Randomised Controlled Trial
RDS	Respiratory Distress Syndrome
RR	Respiratory rate
RR	Risk Ratio
s	second(s)
SCU	Special Care Unit
SD	Standard Deviation
sec	second(s)
SIMV	Synchronised Intermittent Mandatory Ventilation
SIPPV	Synchronised Intermittent Positive Pressure Ventilation
Ti	Inflation Time
Tr	Response Time
TTN	Transient Tachypnea of the Newborn
TTVplus	Targeted Tidal Volume plus
USA	United States of America
VALI	Ventilator-Associated Lung Injury
VAPS	Volume-Assured Pressure Support
VG	Volume Guarantee
VIDD	Ventilator-Induced Diaphragmatic Dysfunction
VILI	Ventilator-Induced Lung Injury
VLBW	Very Low Birth Weight
VT	Tidal volume
VT <sub>e</sub>	Expiratory tidal volume
VTV	Volume-targeted ventilation
WOB	Work of breathing



## **Publications arising from this thesis**

1. **Bhat, P.**, et al. (2015). "Crossover study of proportional assist versus assist control ventilation." Arch Dis Child Fetal Neonatal Ed **100**(1): F35-38.
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3. **Bhat, P.**, et al. (2016). "Volume-targeted versus pressure-limited ventilation in infants born at or near term." Eur J Pediatr **175**(1): 89-95.
4. **Bhat, P.**, et al. (2016). "Prediction of infant extubation outcomes using the tension-time index." Arch Dis Child Fetal Neonatal Ed **101**(5): F444-447.

## **Chapter 1: Introduction**

## **1.1 Background**

### **1.1.1 History and evolution of mechanical ventilation**

Intubation and mechanical ventilation remain important lifesaving tools for neonatal intensive care [1]. It is now a very common modality in intensive care units, and indeed the advent of its use heralded the dawn of modern intensive care units [1,2]. The evolution and clinical adoption of mechanical ventilation has involved considerable speculative discovery and rediscovery and began more than 400 years ago [3]. Primitive use and recorded descriptions of mouth-to-mouth resuscitation, an elementary form of what is now termed intermittent positive-pressure ventilation (IPPV), can be found almost from the beginning of recorded time [4].

Galen, the noted Greek physician and scientist who lived in the second century A.D., played a major role in introducing the importance of structure (anatomy) to the understanding of disease [5]. Although he made great advances, his dissections were limited to animals, and he assumed that the organs of humans and animals were identical [5]. He also studied respiration and taught that breathing was required to maintain the circulation [5]. For the next almost 1,500 years, there were essentially no advances made until the mid-16th century when Vesalius published an excellent treatise on anatomy entitled “De Humani Corporis Fabrica”, which likely had the first definitive reference to positive pressure ventilation as we know it today [6]. In the 17th and 18th centuries, there were a number of approaches used to resuscitate patients but none of them were effective [2]. In 1774, Joseph Priestly and

Willhelm Scheele independently discovered oxygen and subsequently, Lavoisier discovered the importance of oxygen in respiration [2].

In the late 19th century, ventilators based largely on currently accepted physiological principles were developed [7]. Essentially, ventilation was delivered using sub-atmospheric pressure delivered around the body of the patient to replace or augment the work being done by the respiratory muscles. In 1864, Alfred Jones invented one of the first such body enclosing devices [7]. In 1876, Alfred Woillez built the first workable iron lung, called the “spirophore” [8]. The spirophore had a metal rod that rested on the chest; movement of this rod was used as an index of the VT. The first iron lung to be widely used was developed in Boston by Drinker and Shaw in 1929 and used to treat patients with polio [9]. One problem with these devices was that it was extremely difficult to nurse patients because it was difficult to get access to the patient’s body. To address this problem, Peter Lord patented a respirator room, in which the patient lay with her head outside the room [8]; inside, huge pistons generated pressure changes, which caused air to move into and out of the lungs. The respirator room had a door so that the medical staff could enter the ventilator to care for the patient. These ventilators were extremely expensive, so James Wilson developed a ventilation room in which multiple patients could be treated [8], which was used at the Children’s Hospital, Boston, for several epidemics.

The resurgence of polio marked a watershed in the history of mechanical ventilation [2-4]. Before this time, mechanical ventilation was believed to have

some usefulness but was not used widely. Afterward, the benefits of ventilation were dramatic and obvious, leading to its widespread use worldwide [2-4]. Over the past 60 years, many technical aspects of ventilators have dramatically improved with respect to flow delivery, exhalation valves, use of microprocessors, improved triggering, better flow delivery, and the development of new modes of ventilation (e.g., intermittent mandatory ventilation, high-frequency ventilation, volume targeted ventilation, proportional assist ventilation [PAV], neurally adjusted ventilatory assist [NAVA], etc.) [2-4]. In the 1980s and 1990s, there was a paradigm shift from non-synchronized mandatory ventilation to synchronized patient triggered ventilation. The focus has been on improving the interaction between the patient's drive to breathe and the ventilator's delivery of each breath.

Over the last thirty years, the survival of ventilated neonates has improved dramatically with more than 90% surviving the newborn period [10]. The introduction of mechanical ventilation, however, has been associated with a high incidence of complications especially in prematurely born infants, with bronchopulmonary dysplasia (BPD) being a major cause of morbidity [11]. Hence, there is a need to identify the optimum form of ventilation for these infants who are at very high risk of adverse outcomes [1,10]. There is increasing evidence that volutrauma rather than barotrauma causes lung injury and hence there is a need to adopt lung protective strategies right from birth beginning with resuscitation [12-15]. Many current modes that focus on increased patient control of ventilation to the point of allowing the patient to fully drive the ventilator (e.g., proportional modes such as PAV and NAVA).

have been developed in the last few decades and are now commercially available [1]. These latter modes are still under physiological evaluation and are only starting to be tested in clinical trials. Hence, they need appropriate assessment in the neonatal population before being introduced into routine clinical practice.

### **1.1.2 Prematurity: incidence, trends and complications – limited discussion on long term outcome**

Preterm birth rates have been reported to range from 5% to 11% of live births in Europe and other developed countries to 12-13% in the USA [16-18]. Preterm births account for 75% of perinatal mortality [16]. Preterm infants, especially those born less than 28 weeks gestation, are at increased risk of neurodevelopmental impairments and respiratory complications and often require respiratory support in the newborn period [16]. It has been reported that approximately 5% of preterm births occur at less than 28 weeks', about 15% at 28–31 weeks', about 20% at 32–33 weeks' and 60–70% at 34–36 weeks' (near term infants) [16].

Over the last few decades, major advances in perinatal care have increased the survival rate of prematurely born infants especially of those born at less than 28 weeks gestation [19]. This is because of technological advances and the collaborative efforts of obstetricians and neonatologists. The use of antenatal steroids and postnatal surfactant has improved the outcome of prematurely born infants with a dramatic improvement in the survival of ventilated neonates especially those born before 28 weeks' gestation [20,21].

The increased survival of prematurely born infants however has been associated with an increase in the incidence of complications with pulmonary disease continuing to be a major cause of illness and death in extreme preterm infants [10].

Bronchopulmonary dysplasia (BPD) may occur in up to 40-50% of very low birth weight (VLBW) survivors [10,22,23] and the rate rises as the gestational age decreases [22]. Bronchopulmonary dysplasia, defined as oxygen dependence for at least 28 days after birth, was originally described as a chronic respiratory disease occurring in preterm newborns with respiratory distress syndrome who had been exposed to high concentrations of inspired oxygen [24,25]. This respiratory disease (now known as 'classical BPD') occurred in relatively large, prematurely born infants and was characterized by intense airway inflammation, disruption of the normal pulmonary structures and lung fibrosis [24,25]. More recently, a more conservative approach to respiratory care with low-pressure mechanical ventilation, antenatal corticosteroids and surfactant replacement has led to this 'classical' form of BPD being replaced by 'new BPD' [25,26]. This novel entity affects extremely preterm infants born several weeks before the pulmonary alveolarization process has begun and, more generally, before the complex mechanism of lung development has been completed. As a result, 'new BPD' is characterized by injuries occurring in the canalicular and saccular phases of lung development, which disrupt its subsequent alveolarization and vascularization [25,26].

The National Institute of Child Health and Human Development (NICHD)

defined BPD in a consensus statement in 2001[27]. This definition uses supplemental oxygen requirement for 28 days and then identifies three grades of severity, dependent on the respiratory support required at either 36 weeks postmenstrual age (PMA) or at discharge for those born at <32 weeks gestation or at 56 days of life or discharge for those born at >32 weeks gestation [27] [table 1.1]. This definition was validated preliminarily with the NICHD Neonatal Network database and data from Palta et al. [28] and is thought to more accurately identify the risk of adverse outcomes than previous definitions [27].

Gestational Age	< 32 weeks	>32 weeks
Time of assessment	36w PMA or discharge home*	>28d but <56d postnatal age or discharge home*
<b>Treatment with &gt;21% oxygen for at least 28 days plus:</b>		
Mild BPD	Breathing room air at 36w PMA or discharge home*	Breathing room air at 56 days postnatal age or discharge home*
Moderate BPD	Need for <30% oxygen at 36w PMA or discharge home*	Need for <30% oxygen at 56 days postnatal age or discharge home*
Severe BPD	Need for > 30% oxygen with or without positive pressure ventilation or CPAP at 36w PMA or discharge home*	Need for > 30% oxygen with or without positive pressure ventilation or CPAP at 56 days postnatal age or discharge home*

**Table 1.1: Diagnostic criteria for defining BPD [27].**



BPD is associated with long-term respiratory morbidity with many affected infants requiring supplementary oxygen for months or even years after birth [11]. Affected infants are also more prone to respiratory infections and recurrent troublesome wheeze [23]. Children with BPD have been shown to have higher rates of re-hospitalisation [29,30] with some infants requiring as many as 20 readmissions to hospital in the first two years after birth [23]. Children with BPD have also been shown to need longer stays in hospital [31]. Older children may miss school because of recurrent chest infections, troublesome respiratory symptoms and lung function abnormalities, which restrict their physical activity [29]. Extremely low birth weight infants (ELBW) survivors with bronchopulmonary dysplasia have more ill health and hospital readmissions in early childhood than do ELBW infants without bronchopulmonary dysplasia [32]. In ELBW infants with bronchopulmonary dysplasia, differences in lung function can be detected from an early age and may persist into late adolescence [24,33,34].

Northway et al. studied the lung function of 26 adolescents and young adults, born between 1964 and 1973, who had bronchopulmonary dysplasia in infancy, at a mean age of 18 years, and compared the results with those in two control groups: 26 age-matched adolescents and young adults of similar birth weight and gestational age who had not received mechanical ventilation, and 53 age-matched normal subjects [35]. The results showed that 68% of the subjects in the BPD group had airway obstruction, which was fixed in a quarter of those affected. The BPD group also had decreased forced expiratory volume in one second, forced expiratory flow between 25 and 75

percent of vital capacity, and maximal expiratory flow velocity at 50 percent of vital capacity, and increased gas trapping as compared with both control groups ( $P < 0.0001$  for all comparisons) [35]. In a study comparing the lung function of VLBW survivors who had BPD during infancy versus the lung function of VLBW survivors without BPD during infancy, studied at a mean age of 18.9 years, 22% of the cohort had “old” BPD [34]. The results showed that all lung function variables related to airflow were substantially diminished in the VLBW with BPD group as compared to VLBW without BPD in infancy [34]. The rates of asthma were similar in the BPD and the control (non-BPD) groups [34].

During childhood and adolescence, BPD survivors may have respiratory symptoms and lung function impairments closely resembling those of asthmatic patients, though they show a poorer response to inhaled corticosteroids [36]. The mechanism behind obstructive lung function in BPD survivors is different from that of asthma and there is no firm evidence to support an asthma-like inflammatory status [36-38]. The literature tends to suggest that BPD and Asthma do not share the same type of airway inflammation. In fact, although BPD and asthma have some clinical and functional similarities, levels of exhaled nitric oxide and exhaled breath temperature are both lower in BPD survivors than in asthmatic children (a high level of nitric oxide is considered a biomarker of eosinophilic inflammation and responsiveness to corticosteroids). Such data support the hypothesis that airflow limitation in BPD survivors is unrelated to any asthma-like inflammation [36,38], indicating that another pathogenetic mechanism

must be involved [38,39]. Recent reports have also suggested that prematurity may be associated with neutrophilic airway inflammation and oxidative stress later in life [40-42]. Available data thus support the hypothesis that the pathophysiological mechanisms behind airflow limitation in BPD and asthma probably stem from distinct mechanisms [43]. The potentially serious consequences of BPD affecting the health and quality of life of preterm survivors make it important to explore and identify ways to reduce BPD by adopting lung protective ventilatory strategies right from birth beginning with resuscitation.

### **1.1.3 Mortality and Morbidity in infants born at or near term**

Mechanically ventilated term infants comprise approximately 20% of the sick infants admitted to a tertiary NICU unit [44]. Few studies exist on term infants admitted to neonatal intensive care units (NICUs), either examining the risk factors for neonatal morbidity, or the mortality and long-term morbidity of these infants [45-47]. The studies that do exist are mostly retrospective, very few are population-based and more recently have concentrated only on encephalopathy following intrapartum asphyxia [44]. The mortality rate amongst ventilated term-born infants has been reported to range from 9.1 to 11.7% [48] and has been quoted to be high (9.6 to 12.2%) even amongst infants without congenital anomalies [49,50].

Term born infants needing mechanical ventilation represent a mixed group of clinical entities which include transient tachypnea of the newborn (TTN),

meconium aspiration syndrome [MAS], respiratory distress syndrome [RDS], neonatal encephalopathy and 'perinatal asphyxia', usually defined by signs of poor adaptation to the extra-uterine environment [48-50]. Of these, TTN, RDS and MAS represent the leading causes of ventilated respiratory disorders in infants born at term [46,51]. A study of 14813 infants with gestational ages between 37–38 weeks and 50187 infants with gestational ages between 39–41 weeks showed that TTN, RDS and MAS accounted for 36%, 19% and 31% respectively of mechanically ventilated infants [51]. Other less frequent causes for the need for mechanical ventilation included pulmonary infection (7.8%), pneumothorax (3.1%) and primary PPHN (2.3%) [51]. The mortality rate for ventilated term infants in that study was 3.9% and in addition, it was observed that increasing gestational age from 37 to 41 weeks was associated with a significant decrease in incidence of RDS and TTN without any significant change for MAS [51]. Infants with major congenital abnormalities born at or near term represent a small percentage of infants needing mechanical ventilation [49,50,52]. In a large prospectively study of 1011 infants greater than 34 weeks' gestational age, admitted to the neonatal intensive care unit, and requiring assisted ventilation, the incidence of major congenital anomalies was reported to be 21% [52]. The most commonly reported anomalies were gastroschisis (25%), congenital diaphragmatic hernia (15%), tracheo-esophageal fistula (6%), transposition of the great arteries (6%), myelomeningocele (5%), omphalocele (4%) and trisomy 21 (4%) [52]. It is apparent from the above mentioned studies that morbidity in ventilated infants born at or near term is common, yet the evidence from studies examining or comparing ventilatory modes in such infants is limited.

Hence one of the aims of this thesis is to investigate whether volume targeted ventilation is superior to pressure limited ventilation in infants born at or near term.

## **1.2 Resuscitation of prematurely born infants**

### **1.2.1 Volutrauma, the primary determinant of ventilator induced lung injury (VILI)**

In recent years, it has been increasingly recognised that it may actually be the volume of gas delivered to the lungs, and not pressure per se, is more likely to be the primary determinant of lung damage during resuscitation [53-55]. This finding has given rise to the concept of volutrauma. A study [55] was undertaken in preterm lambs evaluating the effect of large volume breaths prior to surfactant administration. One lamb in each of the five pairs of lambs was randomly selected to receive six manual inflations of 35-40 ml/kg before the start of mechanical ventilation, a volume roughly corresponding to the inspiratory capacity of lamb lungs. Following this, both the siblings within the pairs were given rescue porcine surfactant at 30 mins of age [55]. Blood gases and deflation pressure-volume (P-V) curves of the respiratory system were recorded until the lambs were killed at four hours. The results showed that the P-V curves became steeper after surfactant in the control group, but no such effect was seen in those subjected to bagging. At four hours, inspiratory capacity and maximal deflation compliance were almost three times higher ( $p < 0.01$ ) in the controls than in the bagged lambs. The latter were also more difficult to ventilate and tended to have less well-expanded alveoli and more widespread lung injury in histologic sections [55], suggesting

that that only six manual inflations of 35 to 40 mL/kg given to preterm lambs before surfactant administration injured the lungs and reduced the response to subsequent surfactant therapy [55].

In another study [56], anesthetized rats were ventilated with room air at peak inspiratory pressures of 14, 30 or 45 cmH<sub>2</sub>O without any added PEEP, while other rats were ventilated with the same inspiratory pressures but with an added PEEP of 10 cmH<sub>2</sub>O. The results showed that the control group of rats that were not ventilated and the group of rats ventilated with pressures of 14/0 showed no pathological lung changes while the group of rats ventilated on 30/0 and 30/10 had perivascular oedema but no alveolar oedema. Similarly, rats ventilated on 45/10 had no alveolar oedema and survived [56]. On the contrary, rats ventilated with higher pressures of 45/0 cmH<sub>2</sub>O had alveolar and perivascular oedema, severe hypoxemia, and decreased compliance and died within one hour concluding that that interstitial perivascular edema develops from ventilation with high tidal volumes generated by high inflating pressures [56].

A study by Kolobow et al. [57] explored the pulmonary effects of continuous mechanical ventilation (MV) at a peak inspiratory pressure of 50 cmH<sub>2</sub>O in healthy, paralyzed, and anesthetized adult sheep during a period of 48 hours. The 9 control sheep (Group A) were ventilated with 40% oxygen at a tidal volume of about 10 ml/kg and a peak inspiratory pressure of 15 to 20 cmH<sub>2</sub>O. All these animals remained stable throughout the 48 hours of MV with no change in lung function [57]. The 7 sheep in Group B were ventilated with

40% oxygen using a pressure-controlled ventilator at 50 cmH<sub>2</sub>O peak inspiratory pressure, at a VT of 50 to 70 ml/kg. All sheep in Group B developed severe respiratory failure and died or were killed within 2 to 35 h, and showed parenchymal consolidation at autopsy. The 9 sheep in Group C were ventilated as in Group B, except that 3.8% CO<sub>2</sub> was added to the inspired gases: the Group C animals deteriorated more slowly, with little change in PaO<sub>2</sub> but with a severely reduced FRC, VT, total static lung compliance, and grossly abnormal lungs at autopsy. The study concluded that in this model, mechanical ventilation at peak airway pressure of 50 cmH<sub>2</sub>O will lead to progressive impairment in pulmonary mechanics, lung function, acute respiratory failure, and alveolar cellular dysfunction, as demonstrated by highly abnormal minimal surface tension values of saline lung lavage fluid in both study groups [57].

Dreyfuss et al [53] observed significant increases in lung oedema and trans-capillary albumin flux in rats ventilated at high tidal volumes in contrast to rats ventilated with low tidal volumes and high pressures. From the experimental studies [56,57] involving rats and sheep evidence suggests that subtle physiological and morphological alterations, such as alterations of lung fluid balance, increases in endothelial and epithelial permeability, and severe ultrastructural damage, may result from resuscitation, especially when high lung volumes are reached [56,57].

### **1.2.2 Evolution of resuscitation practices during the resuscitation of prematurely born infants**

The pattern of ventilation adopted for newborn resuscitation was based on evolved clinical practice rather than any assessing of efficacy or clinical outcome. In the 1970s and 1980s physiological studies were carried out on the spontaneous onset of ventilation [58-62] and the response to resuscitation [63,64]. Those data, have been incorporated into current international guidelines on neonatal resuscitation [65].

Prematurely born infants often require respiratory support at birth and the degree of support needed is inversely related to their gestational age. These infants are at greater risk of permanent brain damage if effective oxygen delivery is delayed [66]. A lack of lung surfactant makes the lungs of preterm infants very stiff and relatively high inflation pressures may be required to establish effective ventilation and oxygenation [67]. There is increasing animal evidence that even brief exposure to large tidal volumes (as little as three inflation breaths) can result in long term lung damage [14,15, 68].

In a study [15] to evaluate the injury response to a brief period of large tidal volume ventilation, preterm lambs were ventilated with a tidal volume of 15 ml/kg and no positive end-expiratory pressure for 15 minutes to simulate delivery room resuscitation, either with the placental circulation intact or after delivery. After the initial 15 minutes, lambs received surfactant and were maintained with either ventilatory support or placental support for 2 hours, 45 minutes. A control group received no resuscitation and was maintained with



placental support [15] and samples of bronchoalveolar lavage fluid, lung, and liver was analyzed. The results showed that ventilation for 15 minutes with a tidal volume of 15 ml/kg initiated an injurious process in the preterm lung as shown by an increase in inflammatory cells and protein in bronchoalveolar lavage fluid [15]. In addition, subsequent ventilatory support was shown to cause further increases in pro-inflammatory cytokine mRNA and inflammatory cells. In another study [68] evaluating the effect of high tidal volumes and PEEP, operatively delivered preterm lambs were randomly assigned to 4 groups; tidal volume of 15 ml/kg and no PEEP, tidal volume of 8 ml/kg and no PEEP, tidal volume of 15 ml/kg and 5 cmH<sub>2</sub>O of PEEP and tidal volume of 8 ml/kg and 5 cmH<sub>2</sub>O PEEP in the first 15 minutes of birth. The results showed that the markers of lung injury (pro-inflammatory cytokine mRNA IL-1 $\beta$ , IL-6, and IL-8) were significantly elevated in all ventilation groups compared to unventilated controls. In addition, protein Carbonyls, a measure of oxidative injury, and TLR-2 mRNA were also higher in all ventilation groups relative to unventilated controls [68]. No effect of PEEP was found [68]. In a study [14] comparing the consequences of normal tidal volume ventilation in mechanically ventilated rats at a high airway pressure (HiP-LoV) with those of high tidal volume ventilation at a high (HiP-HiV) or low (LoP-HiV) airway pressure and the effects of PEEP (10 cm H<sub>2</sub>O) on both oedema and lung ultrastructure, pulmonary oedema was assessed by extravascular lung water content and microvascular permeability by the dry lung weight and the distribution space of <sup>125</sup>I-labeled albumin. The results showed that HiP-LoV rat lungs were not different from those of controls (7 cm H<sub>2</sub>O peak pressure ventilation). By contrast, the lungs from the groups subjected to high volume

ventilation had significant permeability type oedema. This oedema was more pronounced in LoP-HiV rats. It was markedly reduced by PEEP, which, in addition, preserved the normal ultrastructural aspect of the alveolar epithelium. This was in striking contrast to the diffuse alveolar damage usually encountered in this type of oedema [14]. From the above studies [14,15,68], it is clear that large tidal volumes injure the preterm lung causing structural injury to the airspaces, epithelial leaks that result in interference with surfactant function and cause the release of pro-inflammatory cytokines and inflammatory cells. It is therefore important to monitor and avoid the delivery of excessive tidal volumes during the resuscitation of prematurely born infants.

There has been a recent resurgence in interest in resuscitation at birth, particularly of the preterm infant. This has included lung model studies aiming to improve volume delivery [69-71], the use of video cameras during resuscitation [72], and the role of nasal continuous positive airway pressure (nCPAP) as an alternative to intubation [73]. In a randomized trial [73] investigating whether nasal continuous positive airway pressure, rather than intubation and ventilation, shortly after birth would reduce the rate of death or bronchopulmonary dysplasia in very preterm infants, 610 infants born at 25-to-28-weeks' gestation were randomly assigned to CPAP or intubation and ventilation at 5 minutes after birth and outcomes at 28 days of age, at 36 weeks' gestational age, and before discharge were assessed [73]. The results showed that early nasal CPAP did not significantly reduce the rate of death or bronchopulmonary dysplasia, compared with intubation. The incidence of

pneumothorax was found to be higher in the CPAP group as compared to the intubation group (9% versus 3%,  $p < 0.001$ ). In the CPAP group, however, fewer infants received oxygen at 28 days of life and they needed fewer days of ventilation [73]. In a retrospective cohort study [74] to investigate whether changing to early NCPAP while maintaining a low threshold for intubation for surfactant reduced the need for intubation in very preterm infants, two cohorts of preterm infants were compared retrospectively before and after the introduction of selective intubation and use of early NCPAP [74]. The primary outcome measure was need for intubation less than 72 hours of age and bronchopulmonary dysplasia (BPD) was a secondary outcome [74]. The results showed that although the rate of intubation in the delivery room (69% vs. 46%,  $p < 0.001$ ) and within 72 hours of age (73% vs. 57%,  $p < 0.001$ ) was lower in the cohort of infants treated with selective intubation and use of early NCPAP, there was no reduction in the incidence of BPD (14.3% vs. 15.2%,  $p = 0.82$ ) [74]. A systematic review and meta-analysis [75] to assess whether giving early surfactant with planned brief mechanical ventilation followed by prompt extubation (to NCPAP) is better than selectively giving surfactant when RDS has worsened causing respiratory insufficiency necessitating mechanical ventilation identified six randomised controlled trials reported between 1994 and 2006. The results from this Cochrane review showed that the strategy of early surfactant administration with extubation to NCPAP was associated with significant reductions in the need for mechanical ventilation, fewer air leak syndromes (such as pneumothorax) and a lower incidence of BPD compared with a strategy of later selective surfactant administration and continued mechanical ventilation in infants with RDS [75].

In a prospective study [76] undertaken to identify whether the early use of nasal continuous positive airway pressure (n CPAP) would reduce the rate of endotracheal intubation, mechanical ventilation and surfactant administration, a total of 72 preterm infants at 25-30 weeks gestation who needed respiratory support at five min after birth were randomly assigned to the very early CPAP (initiated five min after birth) or to the late CPAP (initiated 30 min after birth) treatment groups. The primary outcomes were need for intubation and mechanical ventilation during the first 48 hours after birth and secondary outcomes were death, pneumothorax, intraventricular hemorrhage, duration of mechanical ventilation and bronchopulmonary dysplasia [76]. The results showed that there were no significant differences between the two groups with regard to mortality rate, bronchopulmonary dysplasia and patent ductus arteriosus. However, in the early CPAP group, the need for surfactant administration was significantly reduced ( $P = 0.04$ ) and the infants required intubation and mechanical ventilation less frequently than infants in the delayed CPAP group [76]. From the above studies [74-76] one can see that the use of nCPAP at birth was associated with a reduction in the need for intubation and ventilation but there was no reduction in the incidence of BPD.

The use of prolonged inflations during the first few breaths after birth to establish functional residual capacity and reduce lung injury have been studied in small studies and in animal models [61,62,77]. However, these studies are small and limited in number [61]. A study [61] comparing an initial inflation of 5 seconds to the conventional 2 seconds [61] to see if sustained

inflation of 5 seconds led to a reduction in pulmonary inflammation (determined by quantification of IL6, 10 and Ib and TNF a in BAL), demonstrated no apparent benefit [61]. In contrast, in a large randomised controlled trial of resuscitation in preterm infants a peak inflation pressure of 20 to 25 cm H<sub>2</sub>O sustained for 20 seconds followed by nCPAP led to a reduction in the incidence of BPD compared to conventional resuscitation [62]. In a study [77] investigating whether a sustained inflation (SI) to recruit FRC would decrease lung injury from subsequent ventilation, fetal preterm lambs were randomized to one of four 15-min intervention groups: group 1 was given positive end-expiratory pressure (PEEP) of 8 cmH<sub>2</sub>O, group 2 was given 20 second sustained inflation to 50 cmH<sub>2</sub>O followed by a PEEP of 8 cmH<sub>2</sub>O, group 3 was given mechanical ventilation with a tidal volume (VT) of 7 ml/kg and group 4 was given 20 seconds sustained inflation followed by ventilation with a VT of 7 ml/kg [77]. The results showed that SI achieved a mean FRC recruitment of 15 ml/kg (range 8–27 ml/kg). Fifty percent of the final FRC was achieved by two seconds, sixty five percent by five seconds, and ninety percent by 15 seconds, demonstrating prolonged SI times are needed to recruit FRC [77]. SI alone released acute-phase proteins into the fetal lung fluid and increased mRNA expression of pro-inflammatory cytokines and acute-phase response genes in the lung and mechanical ventilation further increased all markers of lung injury suggesting that SI before ventilation, regardless of the volume of FRC recruited, did not alter the acute-phase and pro-inflammatory responses to mechanical ventilation at birth [77]. In a study of 52 infants of less than 31 weeks gestation, resuscitated at birth using either a sustained lung inflation of five seconds or a conventional lung

inflation of two seconds for the first inflation breath the short and long term outcomes were examined [61]. Evidence of pulmonary inflammation was determined by quantification of interleukins 6, 10, and 1b and tumour necrosis factor Alfa in bronchoalveolar lavage fluid by enzyme linked immunosorbent assay. The findings from the study showed no significant effect on the short or long term outcomes between the inflation groups as assessed by BAL fluid cytokine concentrations [61]. In a subsequent study by te Pas et.al, a prolonged inflation time of 20 seconds was associated with a significant reduction in the need for intubation within 72 hours of birth and a lower incidence of chronic lung disease [62]. However, in that study, in addition to the prolonged inflation time, a PEEP of 5-6 cm H<sub>2</sub>O was used which could have partly explained the effect. Hence, it is not very clear whether prolonging the inflation time alone during the first few breaths during resuscitation of prematurely born infants offers any benefit and hence one of the aims of this thesis is to explore the optimal inflation times during the resuscitation of prematurely born infants.

### **1.2.3 Studies of physiological recordings undertaken in prematurely born infants using a respiratory function monitor**

During neonatal resuscitation, traditionally, the adequacy of ventilation during positive pressure ventilation (PPV) in the delivery room (DR) has been assessed by adequacy of chest rise and increased heart rate [78,79]. However, observational studies in the delivery room have demonstrated that observation of chest rise movements to assess positive pressure ventilation is imprecise [80,81]. In comparison, a respiratory function monitor has been

used to provide objective measurements of continuously measured respiratory parameters [57,58,81-84]. It continuously displays graphical waveforms and numerical values of peak inflation pressure (PIP), positive end-expiratory pressure (PEEP), tidal volume (VT), leak around an endotracheal tube (ETT), minute ventilation, respiratory rate, and inspiration and expiration times [58,59,82-85]. RFM can aid training and resuscitations by adding objectivity to the assessment [82].

Recently undertaken studies [58,59,85] by our research group have investigated physiological recordings during the resuscitation of preterm infants. A NM3 respiratory function monitor recorded and displayed the inflation pressures, tidal volumes, flow and end tidal CO<sub>2</sub> using an inline device situated between the inflation device and either a facemask or an endotracheal tube [58,59,85]. In addition, a separate device recorded the infant's heart rate and transcutaneous oxygen saturation levels simultaneously. The results from the studies showed that despite the clinicians having undergone a recognised resuscitation-training course and the neonatal unit having a standard protocol, during the first five inflations delivered by bag and mask resuscitation of prematurely born infants, there was a wide variation in the expired tidal volumes, inflation times and inflation pressures [85]. The median expired tidal volumes achieved in the first few breaths for passive inflations was 2.1 ml/kg and many not exceeding 2ml/kg in excess of one anatomical dead space [85]. Facemask resuscitation was associated with median leak of 55% while endotracheal ventilation was associated with a leak of 10% [85]. The first effective inflation i.e. in excess of

4.4 ml/kg (i.e. twice the anatomical dead space) was almost always associated with the infant's first inspiratory effort, which occurred during inflation and represented a Head's paradoxical reflex (active inflation) [85].

Currently, the UK resuscitation council recommends that during the resuscitation of prematurely born infants, for the first five inflation breaths, inflations should be sustained for 2-3 seconds [60]. However, a more recent study, demonstrated that during the resuscitation of prematurely born infants, neonatal staff rarely maintain the first five inflations for more than one second [59]. This may not be important, as inflation flow usually terminates after 0.3 seconds and there was no relationship between initial flow inflation time and tidal volume [59], however this needs further investigation. From the above-mentioned studies [59-62], it remains unclear as to what the ideal inflation times are, during the resuscitation of prematurely born infants and hence one of the aims of this thesis is to identify if maintenance of the first five inflations for 2-3 seconds will lead to higher tidal volumes and  $\text{ETCO}_2$  levels.

End tidal  $\text{CO}_2$  monitoring provides a potentially useful method for monitoring the onset of effective ventilation. Soon after birth,  $\text{CO}_2$  elimination is only possible if there is a combination of effective aeration of the lungs and pulmonary blood flow [58]. Studies have demonstrated that in infants breathing spontaneously [63] and infants who required intubation in the delivery suite [62], expired end tidal  $\text{CO}_2$  was rarely detected until the infants made a spontaneous breath, suggesting that the infant's inspiratory effort influenced pulmonary vascular dilatation and consequently an increased



pulmonary blood flow leading to the delivery of carbon dioxide to the lungs. In a recent study, it was observed that during the resuscitation of prematurely born infants, the end tidal CO<sub>2</sub> levels rarely exceeded 0.5 kPa before the first active inflation, providing further support that initial resuscitation is ineffective before the active inflation [58]. During the first active inflation, the end tidal CO<sub>2</sub> rose to a mean of 4kPa, indicating that pulmonary blood flow had also increased [58]. In addition, in that study it was shown that the passive inflations following the active inflation had higher expired tidal volumes and expired end tidal CO<sub>2</sub> levels, suggesting that the pulmonary vasodilatation was maintained following the first active inflation [58]. Overall, the main conclusions from the above mentioned studies [58,59,85] were that the current recommended inflation pressures, incorporating PEEP and the inflation times are inadequate for the resuscitation of prematurely born infants and successful outcome depends on the infant making a reflex response. Therefore, one of the aims of this thesis was to assess whether higher compared to lower inflation pressures and/or longer compared to shorter inflation times resulted in higher tidal volumes and end tidal CO<sub>2</sub> clearance.

### **1.3 Ventilatory support in neonates**

Pressure limited mechanical ventilation (PLV) was one of the first ventilation modes used to support infants and is still used extensively worldwide and known as “conventional ventilation”. Introduction of mechanical ventilation was lifesaving, but there were complications particularly if there was an asynchrony between an infant’s spontaneous breathing and the ventilator inflation [65], which led to pneumothorax and intracerebral haemorrhage.

Physiological studies, have demonstrated that those complications could be reduced if faster inflation rates were used which matched the infants' spontaneous respiratory activity [86] and promoted synchrony (the infant breathing in time with ventilator inflations). Subsequently, ventilatory modes (assist/control (A/C) or synchronous intermittent mandatory ventilation (SIMV)) in which ventilator inflations could be triggered by the infant (patient triggered ventilation) were introduced [87, 88].

In A/C mode the infants can trigger ventilator inflation with each of their own breaths [88], but in SIMV only a preset number of ventilator inflations can be patient triggered [87]. It was hoped A/C and SIMV would be even more likely than CMV to promote a synchronous interaction and further reduce complications. Early studies [88] demonstrated that patient triggered ventilation compared to conventional ventilation was associated with improved gas exchange, less asynchrony, reduced blood pressure and cerebral blood flow fluctuations. No positive long-term effects, however, were highlighted by the meta-analysis of the subsequent randomised trials [87].

#### **1.4 Volume targeted ventilation (VTV)**

Traditionally, neonatal ventilation and the control of arterial carbon dioxide levels ( $\text{PaCO}_2$ ) have been accomplished using time-cycled pressure-limited ventilation (TC-PLV or PLV), wherein the clinician selects the peak inspiratory pressure and the inflation time, and the ventilator provides each breath without exceeding this set pressure limit [88,89]. During PLV, the tidal volume (VT) may fluctuate widely due to the baby's breathing, changes in lung

mechanics and variable endotracheal tube (ETT) leak [89,90]. In recent years, it has been increasingly recognised that it may be the volume of gas delivered to the lungs, and not pressure per se, which is more likely to be the primary determinant of lung damage during mechanical ventilation [53-55]. This finding has given rise to the concept of volutrauma.

In view of the evidence that volutrauma causes lung injury, controlling the tidal volumes delivered with mechanical ventilation rather than the peak pressure is a logical strategy for ventilating newborn infants [91,92]. This has generated interest in volume-targeted ventilation (VTV) during which, a constant volume is delivered with each ventilator breath regardless of changes in the infant's lung function [92]. Many ventilators now deliver consistent tidal volumes either at a pre-set rate or during patient triggered mode with the aim of reducing lung damage (volume targeted ventilation, VTV) [12,13, 90-93].

A meta-analysis of an initial four randomised trials demonstrated that although rates of death and BPD were not significantly different between the two ventilator strategies, VTV was associated with statistically significant reductions in some clinical outcomes especially the duration of ventilation and the pneumothorax rates [93]. However, only 178 infants were included in the meta-analysis and different VTV modes were used in the four trials. The manufacturers of modern ventilators use a variety of methods to achieve VTV resulting in differences in the delivered peak pressure, inflation time, airway pressure waveform and hence mean airway pressure, which all could have an impact on the clinical outcomes [93]. The studies included in the review had used different pressure limited modes including ACV and IMV (control

groups). In addition, some studies varied in the use of triggering between volume targeted and non-volume ventilation targeted strategies, which could have had an impact on the clinical outcomes such as duration of ventilation and airleak [93].

Subsequently, a meta-analysis of results from nine randomised controlled trials (RCTs) recruiting 629 prematurely born infants, demonstrated that VTV compared to pressure-limited ventilation (PLV) was associated with significant reductions in death or BPD, pneumothorax, periventricular leucomalacia (PVL), grade III–IV intraventricular haemorrhage (IVH) and episodes of hypocarbia [12]. Also, the meta-analysis showed that the use of volume targeted ventilation was not associated with an increase in adverse outcomes, the duration of ventilation was found to be significantly shorter in infants supported by VTV and there was a significant reduction in BPD [12]. In the RCTs [97, 99,100] however, a wide range of volume target (VT) levels was used, ranging from 4 ml/kg to 10 ml/kg. A study undertaken in infants born at or near term has shown that the level of VT influences the work of breathing (WOB) with higher levels resulting in a lower WOB [94]. Increasing the level of respiratory support by increasing the VT level could however unfavourably impact on respiratory muscle strength.

Morbidity in ventilated infants born at or near term is common [51,95]. Yet few studies have examined or compared ventilatory modes in such infants [96]. None of the trials in the systematic reviews [12,13,93] included infants born at or near term, and it is, therefore, unclear whether VTV would benefit such a

population. In addition, it is also not clear whether VTV when compared to PLV, would be associated with better respiratory muscle strength, lower thoraco abdominal asynchrony (TAA) and fewer episodes of hypocarbia in infants born at or near term. Hence one of the aims of this thesis is to investigate, in a randomized study of infants born at or near term (> 34 weeks gestation) with acute respiratory distress, whether VTV compared to PLV, using the same ventilator type, was associated with a shorter time to extubation, reduced work of breathing and better respiratory muscle strength.

## **1.5 Proportional Assist Ventilation (PAV)**

### **1.5.1 The concept of proportional assist ventilation**

Conventional modes of patient-triggered ventilation such as Assist Control ventilation (ACV) and Synchronized Intermittent Mandatory Ventilation (SIMV) typically synchronize a preset ventilator cycle to the beginning of the spontaneous inspiratory effort [97,98]. The concept of PAV is different to that of the conventional ventilation modes in that the applied ventilator pressure is servo-controlled throughout each spontaneous breath such that it increases in proportion to the respiratory effort made by the infant. This is achieved by rapid feedback that modulates the ventilator pressure continuously according to the input signals of tidal volume and airflow during the infant's spontaneous breathing [99]. The applied ventilator pressure then responds to the input signals in a proportionate fashion.

During PAV, the ventilator augments the infant's spontaneous breathing

activity while leaving the infant with complete control over all aspects of breathing pattern (tidal volume, inspiratory and expiratory times, and flow) [99,100]. As a result, PAV can be considered to be a sophisticated form of patient triggered ventilation whereby the ventilator is completely in tune with the infant's respiratory efforts thereby promoting synchrony [101, 102]. A further potential advantage of PAV is that the clinician can set various levels of "compensation" or "gain" for the infant's lung function abnormality; this is called "unloading" [102]. The ventilator can provide inflation pressure in phase with the tidal volume change in order to reduce the compliance load (i.e., the load due to the stiffness of infant's lungs) and in phase with the flow change to reduce the resistance load (ie, the load due airflow obstruction), termed elastic and resistive unloading, respectively [102]. Various names have been suggested in the literature for the same basic principles: 'Negative ventilator impedance', 'Negative ventilator compliance and resistance', 'Resistive and elastic unloading' and 'Proportional Assist ventilation [100-106].

### **1.5.2 Elastance and Resistance unloading during PAV**

During PAV, depending on the degree of "unloading" chosen, the system can fully compensate for disease-related changes in respiratory system compliance and resistance, such that the respiratory load and the work of breathing return to normal, enabling the infant to use a breathing pattern as if there were no lung disease [102,108]. During mechanical ventilation, generally three factors affect the delivery of gas into the lungs; the elastic (compliance), resistive (resistance) and the inertial components of the respiratory system [107]. The inertia of the respiratory system reflects the

energy needed to accelerate the respiratory system from its stationary phase at the beginning of inflation and is usually small and inconsequential [107]. The compliance of the respiratory system, which reflects the stiffness of the lung, is directly in phase with the volume change while the resistance of the respiratory system, which mainly reflects the resistance offered by the airways during gas flow, is directly in phase with the flow [107]. During PAV, the ventilator has the facility to provide inflation pressure in phase with the tidal volume change to reduce the compliance load, and in phase with the flow to reduce the resistance load or a combination of both. This is defined as elastic and resistive unloading [107].

During ventilation, support is only needed during inspiration as expiration is passive and is driven by the elastic recoil of the lungs. During PAV, the ventilator can track the tidal volume and increase the circuit pressure in proportion to the inspired tidal volume. The ratio of increase in ventilator pressure per unit of tidal volume (gain), called “elastance unloading”, is clinician-adjustable. It determines the degree of unloading and the partition of elastic work of breathing between infant and ventilator. During expiration, the ventilator pressure is returned to the preset positive end expiratory pressure (PEEP) level [106-108]. During PAV, the ventilator also offers the provision to reduce the “resistance load” by providing a negative inflation pressure in phase with a change in flow (resistance unloading) [107,108]. High resistance can delay emptying of the lungs and hence providing a negative pressure can help the infant by reducing the need for active respiratory efforts [107]. Resistive unloading facilitates both inspiratory and expiratory airflow. It does

not, however, initiate the cycle. By adjusting the gain, the clinician can determine the degree of relief of resistive work of breathing needed [106,108].

Although the ventilator measures both compliance (reciprocal of elastance) and the resistance, clinicians can decide if they wish to set the elastance unloading or resistance unloading or both [107,108]. From the limited number of studies in neonates, it remains unclear as to what is the optimal level of elastance and resistance unloading in a variety of respiratory disorders. Prior to undertaking any clinical study, it is essential to optimise PAV delivery and identify the most appropriate levels of unloading in the various clinical scenarios and hence one of the aims of this thesis is to investigate the effects of increasing resistive unloading in a model with high resistance through the measurement of changes in the work of breathing in the dynamic lung model.

### **1.5.3 In-vitro and clinical studies of PAV in neonates**

PAV has been slow to be adopted by clinicians since Schulze and colleagues [109] first recommended it in 1998. Since then, only a few in-vitro and short-term clinical studies have been undertaken. Nevertheless, the results of those studies were promising [99, 105, 107, 110]. In a crossover study comparing PAV with assist control ventilation (ACV) and intermittent mandatory ventilation (IMV) in very low birth weight infants with acute respiratory illness, 36 infants were exposed to 45-minute epochs of ACV, IMV and PAV in a random order [99]. When compared to ACV and IMV, PAV was associated with lower mean airway and peak inspiratory pressures and a 28% reduction in oxygenation index [99]. In addition, no adverse events such as runaway



high pressures were noted during the study. In that study, during the PAV mode, both elastance and resistive unloading was set. The resistive unloading component was uniformly set at 20 cm H<sub>2</sub>O/L/s for all infants aiming to compensate for the resistance of the infants' endotracheal tube [99].

An in vitro study using a lung model has [111] demonstrated that a high level of elastance unloading resulted in very high inflation pressures. The high pressures could be prevented by limiting the peak inflation pressures, but resulted in abnormal pressure waves likely to result in suboptimal oxygenation in vivo. In addition, oscillations appeared in the airway pressure when the level of unloading either fully or overcompensated for the resistance load [111]. In another study [107] using dynamic lung models, the effects of elastance and resistive unloading on inflation pressures and airway pressure waveforms were studied. The results showed that during PAV increasing unloading was matched by an 'inspiratory' load reduction [107]. However, waveform abnormalities and a time lag in delivery of the inflation pressure were noted. The study concluded that the impact of those problems needs careful evaluation in the clinical setting [107].

Another in vitro study [112] investigated the effects of PAV on the elastic work of breathing in-vitro using a dynamic lung model. The results showed that the elastic WOB provided by the ventilator rose from a mean of 0.18 g·cm/ml (SD 0.09) at zero unloading to a mean of 3.75 g·cm/ml (SD 0.24) at an unloading of 2.0 cm H<sub>2</sub>O/ml. The WOB of the lung model fell from a mean of 7.53 g·cm/ml (SD 0.48) to a mean of 2.17 g·cm/ml (SD 0.39). The WOB of the lung

model fell approximately 30% more than the corresponding increase in the WOB provided by the ventilator [112]. In addition, the maximum elastance unloading (2 cm H<sub>2</sub>O/ml) increased the 'effective' compliance of the lung model from 0.4 ml/cm H<sub>2</sub>O (at baseline) to 4.1 ml/cm H<sub>2</sub>O (at maximum unloading) [112]. This would be a high compliance for a 500-gram infant and suggests that 100% elastance unloading may be unnecessary and that 75–80 % of elastance unloading may be sufficient in such an infant [112]. Limiting the amount of unloading would reduce the inflation pressure generated and hence the likelihood of volutrauma [112]. The study concluded that elastance unloading during PAV is very effective in reducing the elastic WOB and should be useful during neonatal respiratory support for infants whose main lung function abnormality was a low compliance. Maximum elastance unloading, however, may be unnecessary.

Infants with evolving or established BPD can have severe lung function abnormalities [28] and it would seem likely that “unloading” might be particularly helpful in such infants. In a randomised crossover study involving 22 extremely low birth weight babies with evolving BPD, one 4-hour period was applied on each of the two consecutive days and compared with epochs of standard PTV [110]. The results showed that the gas exchange was maintained at lower mean and peak inspiratory pressures on PAV compared to PTV ( $p<0.001$ ) [110]. The FiO<sub>2</sub> and the pulse oximetry readings were not different between the two groups, but the desaturations lasted longer on PAV [110], which is of concern as such infants are at high risk of developing pulmonary hypertension. The desaturations were attributed to apnoea's as an

adequate backup rate was not set in the PAV mode. A limitation of the study was that comparison was made to A/C and SIMV using an airflow-triggering sensor, which may function poorly in BPD infants with a high airways resistance. Comparison of PAV, therefore, needs to be made to other modes of ventilation especially A/C only. It is, therefore, important to determine if use of PAV compared to Assist Control (A/C) ventilation is associated with a lower work of breathing and improved respiratory muscle strength, as well as less hypoxic episodes in infants with evolving BPD.

## **1.6 Predicting extubation outcome in neonates**

Newborn infants need endotracheal intubation and mechanical ventilation for a variety of indications; some of which include prematurity, unstable airway, failure of mask airway control, airway abnormalities, prolonged resuscitation and diaphragmatic hernia [113]. It is estimated that approximately as few as one in 500 babies may need intubation at birth [114]. Respiratory failure requiring intubation and mechanical ventilation is common in preterm infants with the need for mechanical ventilation being inversely related to their gestational age. Nearly two thirds of those born at less than 29 weeks gestation will require mechanical ventilation for some duration during the newborn period [115]. It has been reported that infants born less than 33 weeks are 32 times more likely to require assisted ventilation than infants born between 38 and 40 weeks' gestation [116,117].

Whilst mechanical ventilation is often lifesaving, it can be associated with complications such as airway and ventilator-induced lung injury, nosocomial pneumonia and bronchopulmonary dysplasia [113,118,119]. Therefore, it is important that mechanical ventilation be discontinued as soon as the infant is capable of sustaining spontaneous breathing as it has been shown in preterm infants that, survival decreases with more prolonged ventilation [120]. Equally, premature extubation can lead to cardiorespiratory compromise or arrest [121], often needing re-intubation, which in children may prolong the duration of mechanical ventilation and has been shown to be associated with a five times greater risk of mortality than those who are successfully extubated [122,123]. In addition, in a prospective study of neonates, infants and children it was observed that there was a significantly increased risk of moderate or severe airway injury in those that were exposed to recurrent intubations [124].

Successful extubation is often defined as not requiring reintubation during a pre-specified window of observation. The duration of extubation, however, that defines success has not been validated in newborns especially in preterm infants [125]. A systematic review of the definitions of extubation success in very premature infants showed that the duration of observation used to define extubation success ranged from 12-168 hours with 48, 72, and 168 hours (7 days) used most frequently [125]. In a recent neonatal study [126] evaluating the tension time index, extubation failure was defined as a need for re-intubation within 48 hours. As this was the only neonatal study to date evaluating the tension time index, in this thesis, the duration to define extubation success was 48 hours.

Currently, up to 25 to 30% of infants fail extubation [127-129]. The decision to extubate is usually based on clinical assessment, blood gases and ventilator settings but none of these have been found to be reliable [130-133]. It has been reported that upto 40% of the infants weighing less than 1000 grams who are extubated on the above criteria require reintubation [131]. Clinical judgement regarding the timing of extubation remains a challenge for clinicians who must balance the risks of premature extubation with those of prolonged ventilation [123]. In order to overcome the chances of extubation failure, it is essential to identify objective criteria, which accurately predict successful extubation [127].

#### **1.6.1 Predicting extubation outcome using the univariate indices**

A variety of univariate indices have been assessed in an attempt to improve prediction of extubation success including compliance and resistance of the respiratory system, respiratory muscle strength and minute ventilation but none of these have been found to be consistently reliable predictors [119].

Compliance of the respiratory system (CRS), which relates the changes in lung volume to changes in pressure at the airway opening, has been studied as a measure to predict extubation success. CRS measures the combined compliance of both the lung and the chest wall [132] and is measured by an airway occlusion technique [133,134]. Some studies have reported that a higher lung compliance measured prior to extubation amongst very low birth weight infants was predictive of successful extubation [136-139]. Equally,

other studies have found CRS to be a poor predictor of extubation failure [134,135]. A study comparing the results of lung function measurements made before and after extubation to predict extubation success in 30 mechanically ventilated preterm infants, found no significant difference in CRS between the group of infants who remained extubated or failed extubation (median 0.98 (range 0.43 - 1.6) ml/cmH<sub>2</sub>O/kg versus median 0.97 (range 0.58 - 1.26) ml/cmH<sub>2</sub>O/kg,  $p > 0.05$ ) with both a sensitivity and specificity of 50% [134]. Similarly, a study to identify criteria for predicting successful extubation found no significant differences in pre-extubation CRS between infants who did and did not fail extubation (0.88 ml/cmH<sub>2</sub>O/kg versus 0.94 ml/cmH<sub>2</sub>O/kg,  $p = 0.59$ ) [112]. One explanation for the lack of difference in CRS in infants who did or did not fail extubation could have been due to the high use of antenatal steroids and postnatal surfactant therapy, which might have improved the compliance in both the groups [135]. From the recent studies [134,135], it is apparent that CRS is a poor predictor of extubation success, as it does not fully reflect all the pathophysiological processes affecting extubation outcome.

Resistance of the respiratory system ( $R_{RS}$ ) has been investigated as a univariate index to predict extubation failure [128, 136-140]. In a study investigating the pulmonary mechanics of 51 prematurely born infants with RDS, results showed that infants who failed extubation had a significantly higher  $R_{RS}$  values (mean  $\pm$  SD) compared to those who did not ( $221 \pm 27$  cmH<sub>2</sub>O/L/sec versus  $177 \pm 26$  cmH<sub>2</sub>O/L/sec,  $p < 0.001$ ) [136]. Similarly, in a study of 61 mechanically ventilated preterm infants with RDS, the  $R_{RS}$  measured by the passive expiratory flow technique prior to elective extubation

showed that infants who failed extubation had significantly higher  $R_{RS}$  values (mean  $\pm$  SD) than those who were successfully extubated ( $220 \pm 20$  cmH<sub>2</sub>O versus  $170 \pm 10$  cmH<sub>2</sub>O,  $p=0.008$ ) [136]. On the contrary, other studies investigating  $R_{RS}$  as a predictor of extubation success have not found similar significant difference in  $R_{RS}$  values between infants who did or did not fail extubation [140,141]. A lack of difference in the studies is most likely due to the fact that resistance of the respiratory system looks at only one aspect of extubation success rather than reflecting all the pathophysiological processes affecting extubation outcome.

Respiratory muscle strength as measured by maximal inspiratory pressure (P<sub>imax</sub>), has been shown to differ significantly according to extubation outcome [142,143]. P<sub>imax</sub> is the maximal inspiratory pressure during inspiration and is measured using a pneumotachograph by performing brief end expiratory occlusions [142,143]. In a study of 30 infants with a mean gestational age of 35 weeks, the results showed that P<sub>imax</sub> (mean  $\pm$  SD) was significantly higher in infants who were successfully extubated compared to those who failed extubation ( $42 \pm 12$  versus  $24 \pm 7$  torr,  $p<0.01$ ) [161]. Other studies, however, have failed to show similar results with regards to P<sub>imax</sub> as a predictor of extubation success [143,144].

Minute ventilation, a product of tidal volume and respiratory rate, has been explored as predictor of extubation success by a number of studies. Minute ventilation measures the effectiveness of spontaneous breathing and respiratory muscle endurance, and can be easily obtained from real-time

monitoring, now routinely available on most modern ventilators [145]. Some of the observational studies in the 1990s have shown that minute ventilation had a positive predictive value of 86% suggesting that minute ventilation could be useful in predicting extubation outcome [146,147]. In a study of 41 ventilated preterm infants investigating spontaneous minute ventilation as a predictor of extubation success, the results showed that the mean values of spontaneous expiratory minute ventilation were significantly lower in the failure group than in the success group (240 (range 160–353) ml/min per kg versus 309 (range 223–434) ml/min per kg,  $p = 0.0039$ ) [146]. Moreover, the infants in whom extubation failed the length of time spent below the target value of spontaneous expiratory minute ventilation (125 ml/min per kg) was longer when compared with successfully extubated infants ( $p < 0.0001$ ) [146]. Another study demonstrated that although minute ventilation did not improve the rate of successful extubation, it significantly reduced the time to extubation from 36 hours to 8 hours ( $p=0.04$ ) [145]. On the contrary, in a recent study of 50 neonates mechanically ventilated for RDS and deemed ready for extubation as defined by clinical criteria, the results of pulmonary function testing showed no significant difference in spontaneous minute ventilation ( $341 \pm 18$  ml/min/kg versus  $37 \pm 34$  ml/min/kg,  $p > 0.05$ ) between the neonates who were successfully extubated and those who required reintubation [140]. In summary, the evidence from studies have been mixed and minute ventilation has not proved consistently to be a good predictor of extubation outcome.



### **1.6.2 Predicting extubation outcome using the multivariate indices**

Univariate indices have not been consistently reliable in predicting extubation outcomes. This may be because of the fact they only look at one physiological variable to predict weaning and extubation. Extubation success depends on the adequacy of respiratory drive, the capacity of the respiratory muscles and the load imposed upon them [148]. It is therefore likely that composite multivariate indices may be more predictive.

A spontaneous breathing trial (SBT) has been used in adult and paediatric patients for predicting successful extubation [127,149,150] and was found to be a useful test in one study among premature infants [151]. In a neonatal study investigating the accuracy of three tests; minute ventilation, ratio of ET CPAP minute ventilation to ventilator minute ventilation and SBT in predicting successful extubation, ventilated preterm infants considered ready for extubation were switched to endotracheal tube CPAP for three minutes and closely monitored for bradycardia (HR less than 100 bpm) and oxygen desaturations (less than 85%) [151]. The results showed that SBT was found to be the most accurate of the three tests with a sensitivity of 97% and a specificity of 73% in predicting successful extubation [151]. In another neonatal study investigating SBT, 49 ventilated preterm infants spent five minutes on ET CPAP rather than three minutes [135]. The results showed that although SBT had a sensitivity of 92% and a positive predictive value of 88%, the specificity was only 50% [135]. A recent study investigating the predictive value of respiratory variability index (VI), alone and in combination with the SBT, found the predictive values of SBT to be 100% and the specificity to be

63% [152]. In the same study, however, when SBT was combined with variability index of either inspiratory time (TI) or tidal volume (VT) the predictive accuracy of the SBT improved having a specificity to 75% [152].

The Rapid Shallow Breathing Index (RSBI) and CROP index were first developed by Yang and Tobin [153] as multivariate indices to predict extubation success. The RSBI represents the ratio of respiratory frequency to tidal volume ( $f/V_t$ ) and quantitates the extent of the rapid shallow breathing, reported to be a common finding in infants who fail weaning trials [153]. The CROP index is a multivariate index of compliance, respiratory rate, oxygenation and maximal inspiratory pressure ( $P_{imax}$ ) and provides an estimation of gas exchange and the relationship between respiratory muscle reserve and the demands placed upon the respiratory system [153]. Although one study investigating RSBI and CROP indices found that a modified CROP index of more than 0.1ml/kg/weight/breath/min was 100% specific and sensitive in predicting extubation success [154], other studies have shown that the predictive power of these indices in children is poor and inconsistent [155-157]. Hence these indices cannot be used reliably to predict extubation outcome in neonates.

### **1.6.3 Predicting extubation outcome using the tension time index**

Tension time index of the diaphragm (TTdi) and Tension time index of the respiratory muscles (TTmus) are multivariate composite indices that reflect a measure of the load on and capacity of the diaphragm and respiratory muscles respectively and have shown promising results in children and

neonates [125,158]. Bellemare and Grassino first described TTdi in the 1980's [159,160]. TTdi is calculated by relating the mean transdiaphragmatic pressure per breath (Pdi mean) to the maximal inspiratory transdiaphragmatic pressure (Pdimax) and the inspiratory time (Ti) to the total respiratory cycle time (Ttot) and is calculated using the formula  $TTdi = (Pdi_{mean}/Pdi_{max}) \times (Ti/T_{tot})$ , where Pdi<sub>mean</sub> is the average Pdi during inspiration. [125,159]. Studies involving healthy adult volunteers who were required to breathe with a constant respiratory pattern for 45 minutes or until they were unable to maintain a constant transdiaphragmatic pressure (Pdi) showed that the time taken for the diaphragm to fatigue was inversely proportional to the tension time index of the diaphragm [159]. Furthermore, the same studies showed that in adults, a TTdi of greater than 0.15 represents an unsustainable load on the diaphragm [159,160].

The tension time index of the respiratory muscles (TTmus), a non invasive TTI measurement based on airway pressure, was developed as an alternative to the invasive TTdi [161] and used in children [162,163]. TTmus is calculated using the formula  $TTmus = (P_{i_{mean}}/P_{i_{max}}) \times (Ti/T_{tot})$ , where P<sub>i</sub><sub>mean</sub> is calculated as  $P_{i_{mean}} = (5 \times P_{0.1} \times Ti)$  [161-163]. Measuring TTmus can be advantageous as in addition to being non-invasive; it provides information about all the inspiratory muscles as a whole rather than just the diaphragm and therefore may be clinically applicable [164]. In a study involving 80 ventilated children (median age of 2 years) in paediatric intensive care unit, using a predetermined cut-off of greater than 0.15 for TTdi, the sensitivity and specificity of TTdi was found to be 100% in predicting extubation failure [158].

The study also devised a cut-off for TTmus of greater than 0.18 above which the sensitivity and specificity was found to be 100% thus showing that when compared with TTdi, TTmus provided an accurate assessment of the load capacity ratio of the inspiratory muscles in ventilated children avoiding the need to perform invasive measurements [158]. In a pilot study done in a neonatal population, data from 20 infants were retrospectively analysed using previously describe cut-offs (TTdi > 0.15 and TTmus of > 0.18). The results showed that there were significant differences in TTdi and TTmus between those who were and were not successfully extubated [126]. Additionally, a TTdi below 0.15 and TTmus below 0.18 were similarly accurate in predicting successful extubation in infants with 100% specificity and sensitivity. This study, however, was not adequately powered and measurements were taken as part of an on-going randomised trial.

The results from the above-mentioned studies in children and neonates evaluating tension time index as a predictor of extubation success have been promising. There is, however, a need to assess, in an appropriately powered study in infants born at term or prematurely, whether TTdi and/or TTmus predict extubation failure. In addition, due to the lack of evidence from the literature, there is a need to explore the 'optimal' cut-off levels for TTdi and TTmus in neonates with reference to previously described cut-offs'. Hence one of the aims of this thesis is to investigate if extubation failure will be predicted by a tension time index of the diaphragm (TTdi) of greater than 0.15 and tension time index of the respiratory muscles (TTmus) of greater than

0.18 and to identify the optimal cut-offs that accurately predict extubation failure.

## **1.7 Summary**

Prematurely born infants often require respiratory support at birth and the degree of support needed is inversely related to their gestational age. Recently undertaken studies have shown that the current UK Resuscitation Council recommended inflation pressures, incorporating PEEP and the inflation times, are not optimal for the resuscitation of prematurely born infants. There is, therefore, a need to assess whether higher compared to lower inflation pressures and/or longer compared to shorter inflation times resulted in higher tidal volumes and end tidal CO<sub>2</sub> clearance during the resuscitation of prematurely born infants.

In recent years, it has been increasingly recognised that volutrauma and not barotrauma per se, is more likely to cause lung damage during mechanical ventilation. A meta-analysis of studies undertaken in prematurely born infants have demonstrated that VTV compared to pressure-limited ventilation (PLV) was associated with significant reductions in death or BPD, pneumothorax, periventricular leucomalacia (PVL), grade III–IV intraventricular haemorrhage (IVH) and episodes of hypocarbia. None of the studies, however, included infants at or near term. Although morbidity in ventilated infants born at or near term is common, few studies have examined or compared VTV with other

modes in such infants. Hence there is a need to assess whether VTV would benefit such a population.

Proportional assist ventilation (PAV) is a promising new mode of ventilation in which the applied ventilator pressure is servo-controlled throughout the spontaneous breath such that it increases in proportion to the respiratory effort made by the infant. It is therefore essential to identify if proportional assist ventilation (PAV) will be better than assist control ventilation (ACV) in infants with evolving chronic lung disease. In addition, it is also essential to determine the effects of increasing resistive unloading in a dynamic lung model with a high resistance to ascertain the most appropriate levels of resistive unloading.

Predicting the timing of extubation remains a challenge for clinicians. In order to overcome the chances of extubation failure, it is essential to identify objective criteria, which accurately predict successful extubation. Tension time index as a predictor of extubation failure have been promising in children and in a recent pilot study in neonates. There is a need to assess, however, in an appropriately powered study whether in infants born at term or prematurely, TTdi and/or TTmus do predict extubation failure. In addition, due to the lack of evidence from the literature, there is a need to explore the 'optimal' cut-off levels for TTdi and TTmus in neonates with reference to previously described cut-offs'.

## 1.8 Hypotheses

1. During the resuscitation of prematurely born infants, initial pressures of 25/5 cmH<sub>2</sub>O will increase the expired tidal volume and end tidal carbon dioxide levels indicating more effective resuscitation. Maintenance of the first five inflations for 2-3 seconds will lead to higher tidal volumes and ET<sub>CO</sub><sub>2</sub> levels during the resuscitation of prematurely born infants.
2. In infants born at or near term, volume targeted ventilation (VTV) when compared to pressure limited ventilation (PLV), will be associated with shorter time to extubation, reduced work of breathing, increased respiratory muscle strength and reduced asynchrony.
3. In a dynamic lung model representing bronchopulmonary dysplasia, during PAV, resistive unloading will reduce inspiratory load.
4. In infants with evolving chronic lung disease, proportional assist ventilation (PAV) when compared to assist control ventilation (ACV), will be associated with reduced work of breathing, increased respiratory muscle strength and be associated with less ventilator-infant asynchrony and better oxygenation.
5. Extubation failure will be predicted by the tension time index of the diaphragm (TT<sub>di</sub>) of greater than 0.15 and tension time index of the respiratory muscles (TT<sub>mus</sub>) of greater than 0.18.

## 1.9 Aims

1. To compare the effects of inflation pressures of 20/5 cmH<sub>2</sub>O and short inflation times to 25/5 cmH<sub>2</sub>O and long inflation times on tidal volumes and end tidal CO<sub>2</sub> levels during the first five inflation breaths in prematurely born infants.
2. To determine, in a randomized study of infants born at or near term (> 34 weeks gestation) with acute respiratory distress, whether VTV compared to PLV, using the same ventilator type, was associated with a shorter time to extubation. In addition, to assess if any difference in the time to extubation was associated with differences in the work of breathing or respiratory muscle strength between the two groups.
3. To determine the effects of increasing resistive unloading in a model with a high resistance through the measurement of changes in the work of breathing in the dynamic lung model.
4. To determine whether in prematurely born infants with evolving bronchopulmonary dysplasia (BPD), PAV compared to ACV would: reduce the work of breathing of the infant, be associated with increased respiratory muscle strength and be associated with less ventilator-infant asynchrony and improved oxygenation.



5. To determine if extubation failure will be predicted by a tension time index of the diaphragm (TTdi) of greater than 0.15 and tension time index of the respiratory muscles (TTmus) of greater than 0.18.

## **Chapter 2: Methods**

## **2.1 Overview of protocols and ethical approval**

### **2.1.1 Resuscitation study:**

Optimal inflation pressures and times to produce adequate expiratory tidal volumes and end tidal CO<sub>2</sub> levels were assessed in prematurely born infants less than 34 weeks' gestation using a respiratory function monitor (NM3 respiratory profile monitors (RPM), Philips Respironics, Connecticut, USA). The infants were divided according to whether the inflation pressures (PIP-PEEP) they received were less than or greater than 20 cm H<sub>2</sub>O and subdivided according to whether the inflation times were less than or greater than 1.5 seconds. The Outer North London Research Ethics Committee approved the resuscitation study (REC reference number: 09/H0724/38). The Committee required parental consent only for the analysis of the data; this was obtained once the mother was transferred to the postnatal ward. The study was undertaken on the delivery unit at King's College Hospital NHS Foundation Trust, London.

Conducting clinical trials especially in the delivery room with preterm and other sick term neonates is important if care for these groups of vulnerable infants is to be improved and evidence based. Approaching the parents of these infants at such a difficult time is not easy and pose a unique challenge to researchers with regards to obtaining informed consent for such research [165]. If prospective informed consent is to be obtained before birth, many parents who consent for such studies never become eligible [166]. Equally, many babies who require resuscitation and are eligible for delivery room

resuscitation studies will not be enrolled, as parents haven't had enough time or opportunity to give antenatal consent [167].

In a survey [168] undertaken to understand the views and attitudes of international neonatal resuscitation scientists regarding the informed consent practices, investigators of delivery room resuscitation raised concerns about the scientific limitations of studies using antenatal consent. Selection bias was identified as the most common methodological flaw with prospective informed antenatal consent [168]. In view of the above concerns, one alternative to prospective informed antenatal consent is “retrospective” consent or “deferred” consent, in which eligible infants are enrolled after birth, and parents are approached for consent as soon as possible after birth [167]. There is, however, limited description in the literature of the views and attitudes of both the parents of new-borns and the researchers with regards to retrospective consent [168].

### **2.1.2 VTV versus PLV study in infants born at or near term:**

A randomised study was undertaken in infants greater than 34 weeks of gestation to determine whether volume targeted ventilation (VTV) or pressure-limited ventilation (PLV) reduced the time to successful extubation and if any difference was explained by a lower work of breathing (WOB), better respiratory muscle strength or less thoracoabdominal asynchrony (TAA) and associated with fewer hypocarbic episodes. The study was undertaken on the neonatal unit at King's College Hospital NHS Foundation Trust, London and

was approved by King's College Hospital Research Ethics Committee (REC reference number: 07/H0808/147). Written, informed consent was obtained from parents prior to the commencement of the studies.

### **2.1.3 In-vitro assessment of proportional assist ventilation**

The effect of different levels of resistive unloading on the work of breathing (WOB) was investigated using a dynamic lung model. The lung model had a resistance of 300 cm H<sub>2</sub>O/l/s to mimic an infant with bronchopulmonary dysplasia.

### **2.1.4 Randomised crossover study of PAV versus ACV:**

Proportional assist ventilation (PAV) was compared with assist control ventilation (ACV) in prematurely born infants remaining ventilated beyond the first week of life to determine whether the PAV mode was associated with reduced work of breathing and ventilator–infant asynchrony and increased respiratory muscle strength and improved oxygenation. The study was undertaken on the neonatal unit at King's College Hospital NHS Foundation Trust, London and was approved by King's College Hospital Research Ethics Committee (REC reference number: 07/H0808/147). Written, informed consent was obtained from parents prior to the commencement of the studies.

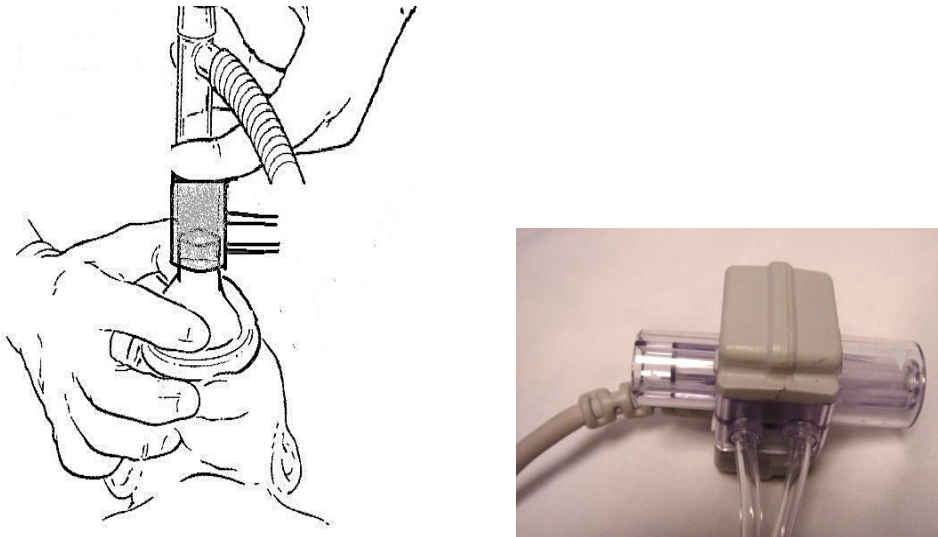
### **2.1.5 Tension time index study to predict extubation outcome**

The accuracy of TTdi and TTmus in predicting extubation outcome in both prematurely and term-born infants was compared to assessments of respiratory muscle strength, respiratory drive, the work of breathing or routinely available clinical data. The optimal cut-off levels determined in the current study were compared to those obtained previously. The study was undertaken on the neonatal unit at King's College Hospital NHS Foundation Trust, London and was approved by London Bromley Research Ethics Committee (REC reference number: 12/LO/2038). Written, informed consent was obtained from parents prior to the commencement of the study.

## 2.2 Respiratory Function Monitoring

### 2.2.1 Equipment

Physiological parameters during resuscitation were recorded using a commercial respiratory function monitor (NM3 respiratory profile monitor (RPM), Philips Respironics, Connecticut, USA). The NM3 respiratory profile monitor had a combined pressure, flow and carbon dioxide (CO<sub>2</sub>) sensor with a dead space of 0.8 ml. The sensor was placed in the resuscitation circuit between the t-piece and the facemask (Figure 2.1). Flow was measured by means of a fixed orifice differential pressure pneumotachometer and CO<sub>2</sub> was measured using a solid-state infrared sensor.



**Figure 2.1: Pneumotachometer with capnostat inserted between the facemask of the infant and the T-piece.**

Differential pressure across the pneumotachometer was measured using a differential pressure transducer located inside the monitor. Airway pressure was obtained using a second pressure transducer connected via a side arm to one of the pneumotachometer pressure lines. The monitor was connected to a laptop (Dell latitude, Bracknell, UK) running customized Spectra software (3.0.1.4) (Grove medical, London, UK) via an analogue to digital cable.

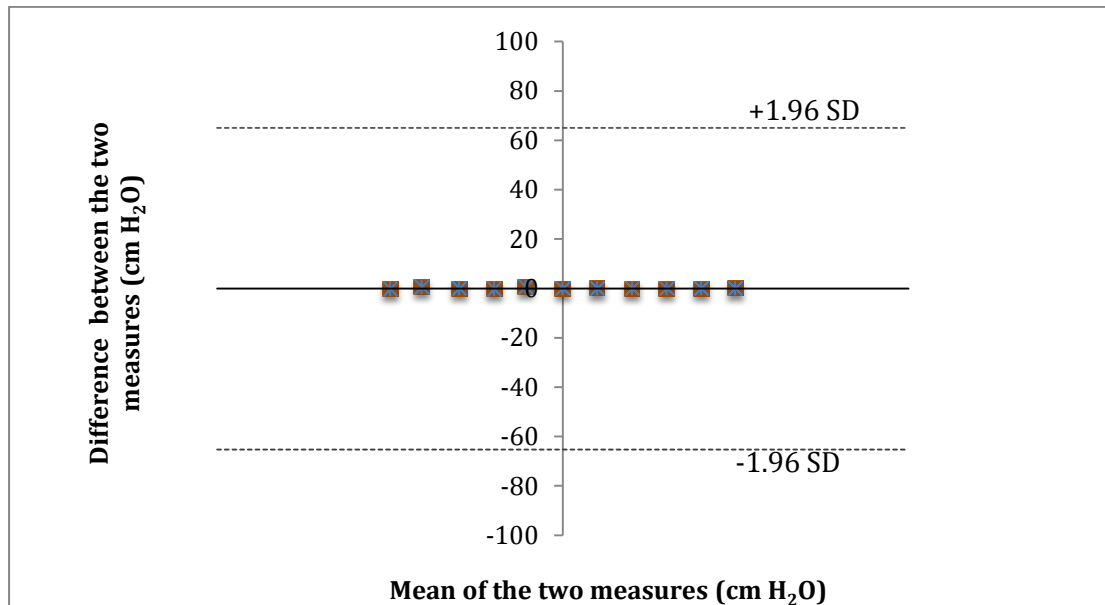
During resuscitation, positive pressure inflations were delivered by a t-piece device (Neopuff Infant resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand) attached to the facemask. The Neopuff, a continuous flow, pressure-limiting device, had a built in manometer, a positive end expiratory pressure (PEEP) valve and a gas flow rate of 5 l/minute. The safety pressure relief valve was set at 30 cm H<sub>2</sub>O

### **2.2.2 Calibration and linearity of respiratory function monitor**

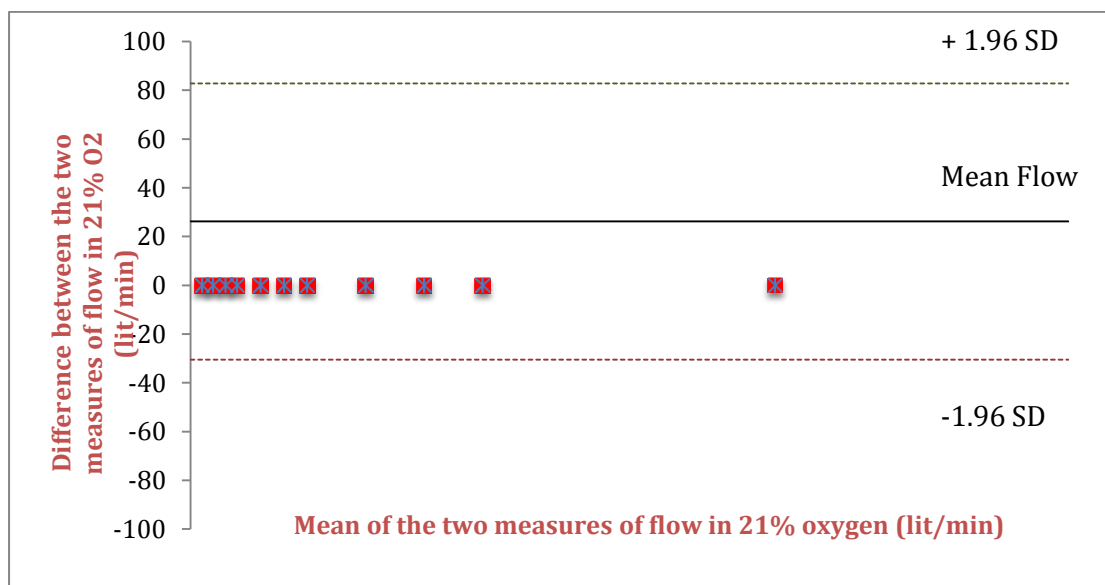
The NM3 monitor was automatically calibrated for flow, pressure and CO<sub>2</sub> according to the factory stored calibration in the monitor. The pressure transducer was automatically 'zeroed' to correct for changes in ambient temperature. According to the manufacturer's information, the accuracy of the flow sensor was  $\pm 3\%$  and the airway pressure was  $\pm 2\%$ . The software compensated for higher oxygen concentrations so that gas density and viscosity effects did not cause significant errors in the flow or volume measurement. The NM3 respiratory profile monitor was assessed using a water manometer and found to give accurate pressure measurements, which were linear across the pressure range (Figure 2.2). In addition, the NM3 was



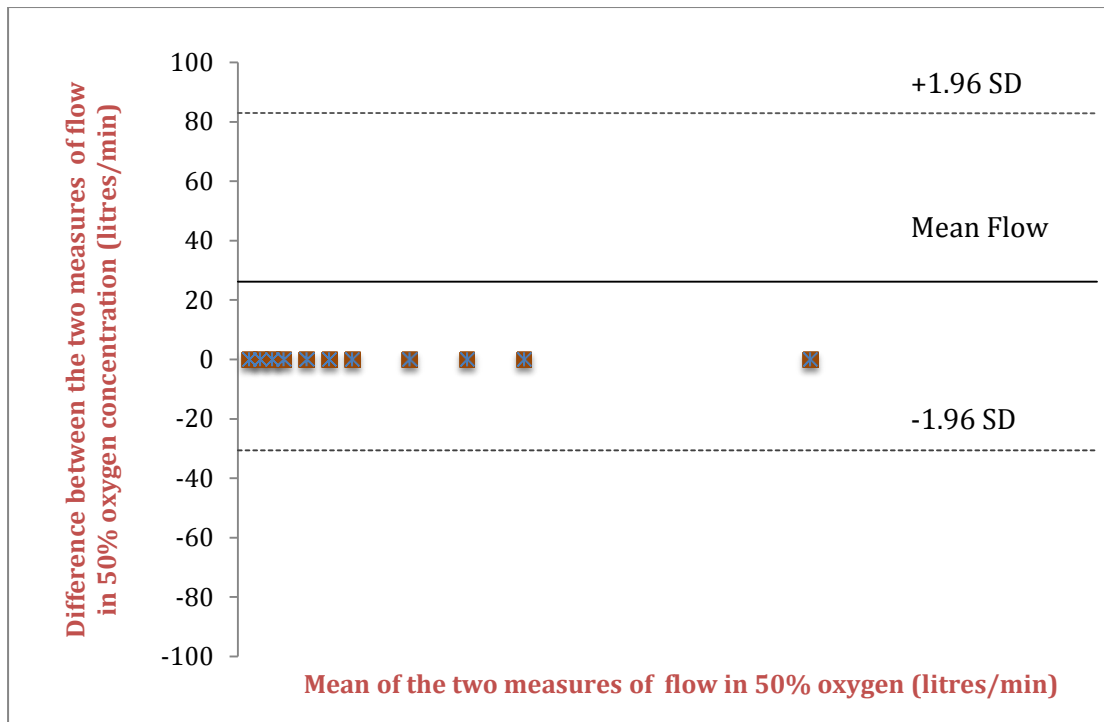
also assessed regarding volume measurements and the inspired oxygen concentration (Figure 2.3 – 2.5) and the  $\text{ETCO}_2$  measurements unit with regard to  $\text{CO}_2$  calibration (Figure 2.6).



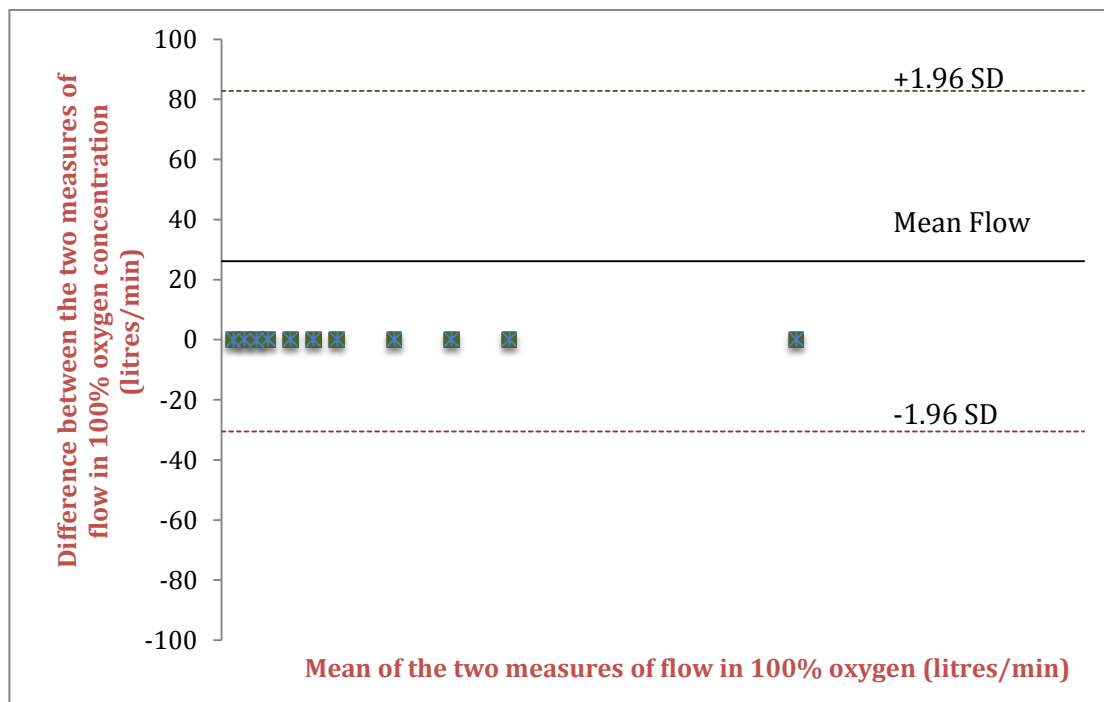
**Figure 2.2: The accuracy of the NM3 pressure transducer tested against a water manometer**



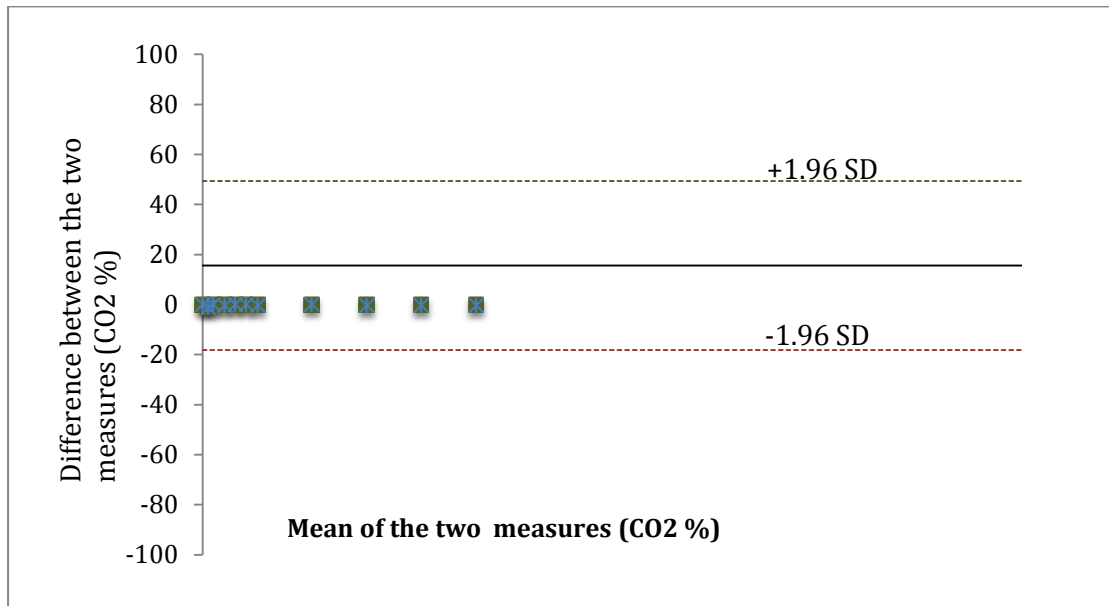
**Figure 2.3: The accuracy of the NM3 flow transducer in 21% oxygen concentration (Bland-Altman analysis)**



**Figure 2.4: The accuracy of the NM3 flow transducer in 50% oxygen concentration (Bland-Altman analysis)**



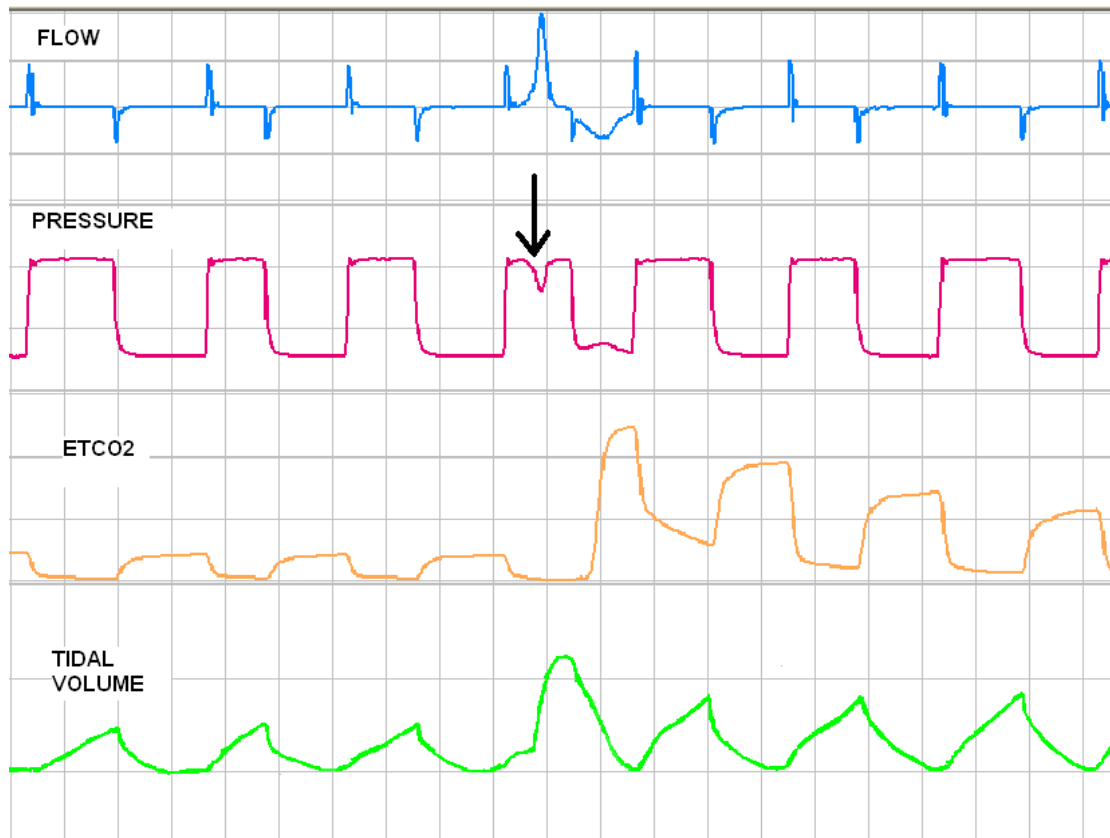
**Figure 2.5: The accuracy of the NM3 flow transducer in 100% oxygen concentration (Bland-Altman analysis)**



**Figure 2.6: The accuracy of the NM3 ETCO<sub>2</sub> Capnograph (Bland-Altman analysis)**

### 2.2.3 Data acquisition

The Spectra software (3.0.1.4) (Grove medical, London, UK) was set to display and record the pressures (PIP and PEEP), flow, tidal volume and end tidal  $\text{CO}_2$  (Figure 2.7).



**Figure 2.7:** A trace obtained from a 26 weeks gestation infant where the infant has taken an active breath. The black arrow points to the inspiratory effort by the infant as identified by the negative deflection of the pressure trace and a positive deflection of the flow trace which is associated with an increase in tidal volume and the end tidal  $\text{CO}_2$

## **2.3 Physiological measurements**

### **2.3.1 Equipment to measure Pgas, Poes, Pdi and PTPdi**

Transdiaphragmatic pressure was obtained from measurements of gastric (Pgas) and oesophageal (Poes) pressures measured using a dual-pressure, transducer-tipped catheter (CTO/2-1, Gaeltec Ltd, Dunvegan, UK). The pressure transducers were five centimeters apart, with the distal transducer located 0.3 cm from the tip of the catheter (Figure 2.8). The catheter was connected to a Gaeltec control amplifier unit (S7D-2, Gaeltec, Dunvegan, UK). The signals were then amplified using a carrier amplifier (CD280, Validyne Corporation, Northridge, California) and acquired and displayed in real-time alongside airway pressure and flow on the data acquisition system with 100 Hz analogue-to-digital sampling.

### **2.3.2 Positioning of the dual pressure transducer tipped catheter**

The dual pressure transducer tipped catheter was inserted either via the infant's nose or the mouth and positioned so that the pressure transducers were located in the lower oesophagus and stomach. The measurement for initial length of insertion was from the tragus of the ear to the middle of the mouth to two centimeters below the xiphisternum. The distal pressure transducer positioned in the stomach provided an estimate of intra-abdominal pressure (Pgas). The proximal pressure transducer positioned in the lower third of the oesophagus provided an estimate of intra-thoracic pressure (Poes). To ensure correct positioning of the transducers, the airway was

briefly occluded and the polarity and magnitude of the Poes and Pgas signals examined. A positive pressure deflection during an occluded inspiration demonstrated that the Pgas transducer was located in the stomach. Correct positioning of the oesophageal transducer was determined by comparison of Poes to airway pressure (Paw) obtained from the side arm of the pneumotachograph during the occlusion. Agreement between Poes and Paw within 94-103% demonstrated that the Poes transducer was correctly positioned in the lower third of the oesophagus [169,170]. The catheter was secured once the correct positioning was confirmed.

### **2.3.3 Calibration and linearity of Gaeltec control amplifier unit and transducers (Pgas and Poes)**

A two-point calibration of the Pgas and Poes transducers and the Gaeltec control amplifier unit was undertaken prior to each measurement. The linearity of the Pgas and Poes transducers was assessed by plotting the digital output (A/D units) from the analogue to digital converter against applied pressure measured with a C950315 pressure meter (Comark, Welwyn Garden City, UK). The linearity of oesophageal and gastric transducers were assessed across the range of -50 to +50 cmH<sub>2</sub>O in 10 cmH<sub>2</sub>O increments and were found to be linear (Figure 2.8 and Figure 2.9).

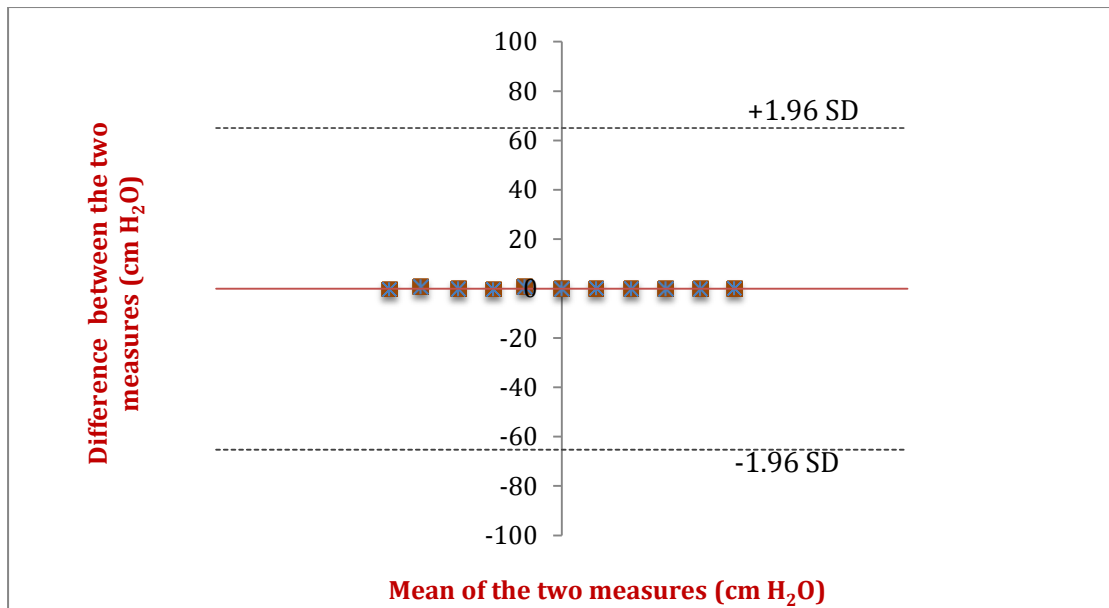


Figure 2.8: Linearity of the oesophageal transducer against the comark pressure meter (Bland Altman plot)

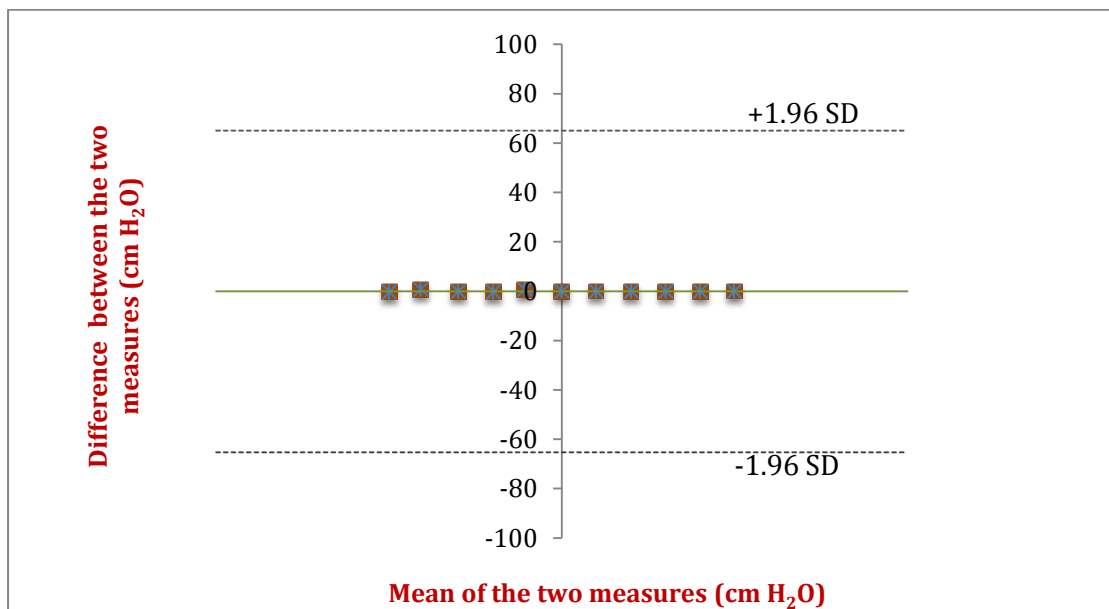


Figure 2.9: Linearity of the gastric transducer against the comark pressure meter (Bland Altman plot)

#### **2.3.4 Equipment for measuring airway pressure and flow**

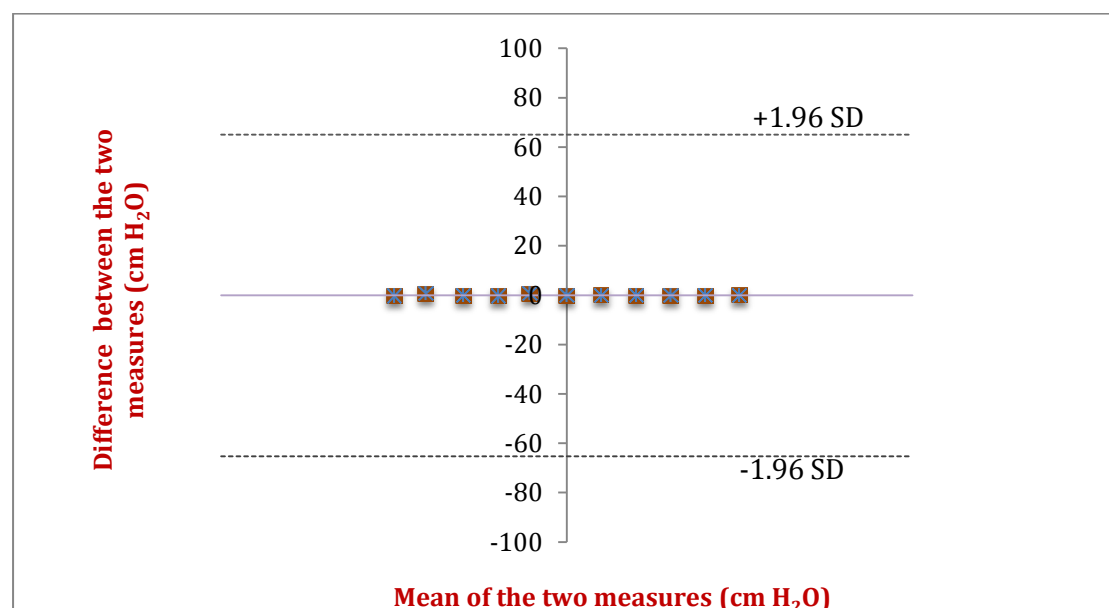
Airflow was measured using a pneumotachograph (Mercury F10L, GM Instruments, Kilwinning, Scotland) inserted between the infant's endotracheal tube and the ventilator manifold. Pressure drop across the pneumotachograph was measured using an appropriate range differential pressure transducer (MP45, range  $\pm 2$  cm H<sub>2</sub>O, Validyne, Northridge, CA, USA). Airway pressure (Paw) was measured from a side port on the pneumotachograph using a second a differential pressure transducer (MP45, range  $\pm 2$  cm H<sub>2</sub>O, Validyne, Northridge, CA, USA). The measured deadspace of the pneumotachograph with the attached tubing was 1 ml.

The signals from the flow and airway pressure transducers were amplified (CD 280, Validyne, Northridge, CA, USA) and subsequently recorded and displayed in real time either on a laptop (Latitude CPi Dell Inc, Round Rock, Texas, USA) or desktop computer (Optiplex 170L, Dell Inc, Round Rock, Texas, USA) running a custom written software application (Labview Version 5.0, National Instruments, Austin TX, USA) with 100 Hz analogue to digital sampling (16 bit DAQ card, DAQ 6036E, National Instruments, Austin TX USA for the laptop or PCI-MIO-16XE-50, National Instruments, Austin TX, USA for the desktop).

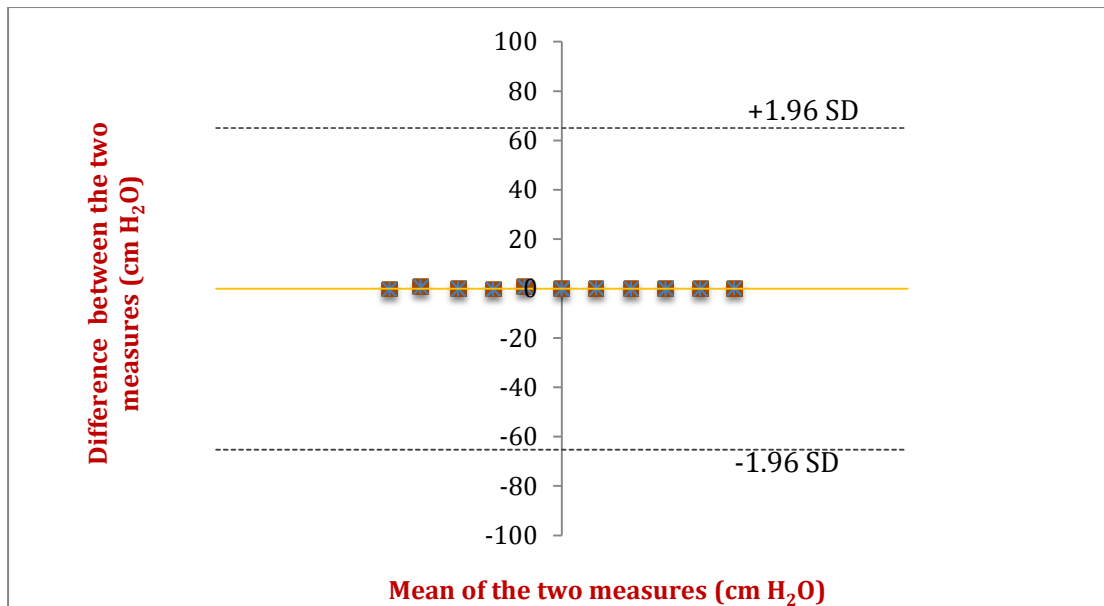


### 2.3.5 Calibration and linearity of airway pressure transducer

Prior to each measurement, the airway pressure transducer was calibrated using a portable pressure meter (C950315, Comark, Welwyn Garden city, UK). The linearity of the Comark pressure meter was tested against a water manometer, and was linear across a range of pressures from -450 to 450 mm H<sub>2</sub>O (figure 2.10). Linearity of the airway pressure transducer-amplifier system was assessed by applying pressures across the range -200 to 200 cmH<sub>2</sub>O using the digital pressure meter to transducer and plotting the amplified electrical output against actual delivered pressure. The system was found to be linear across a range of applied pressures (Figure 2.11).



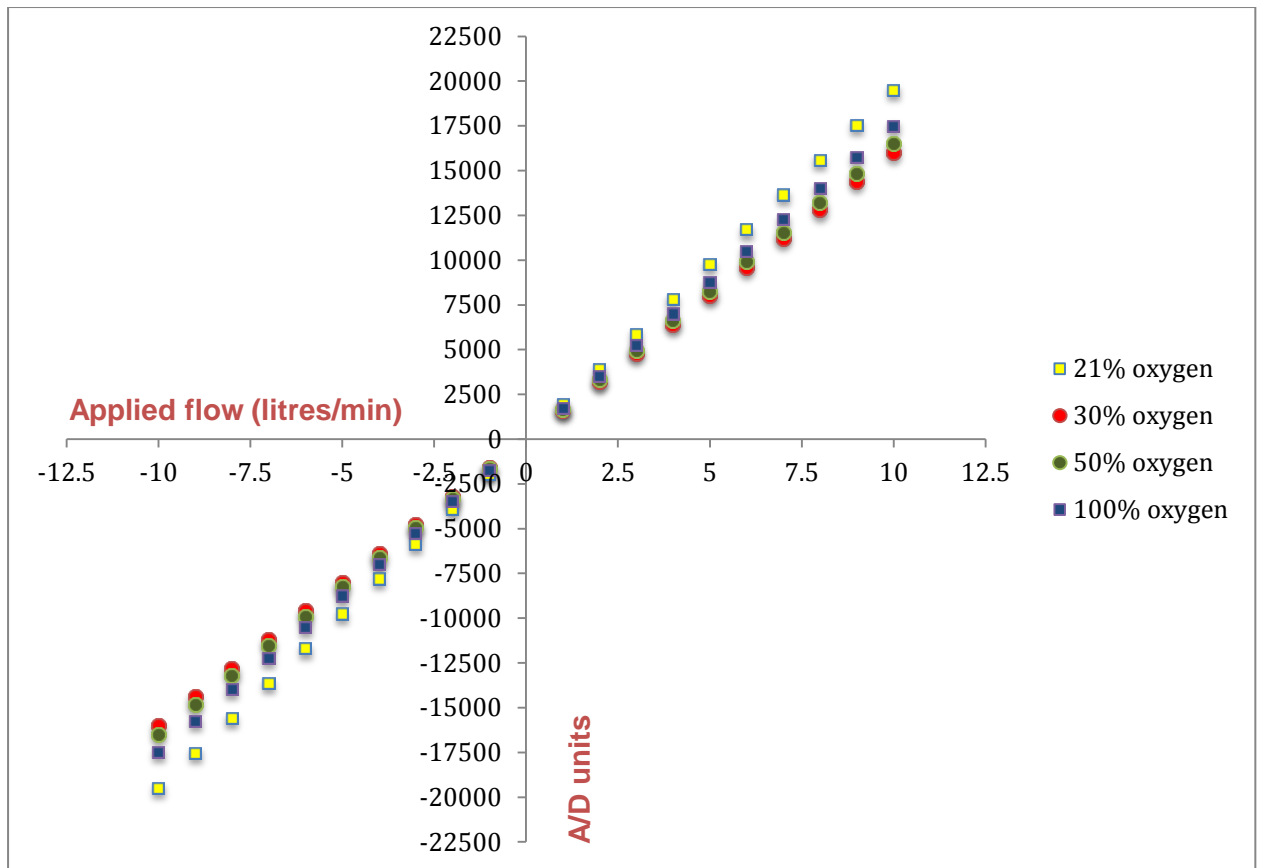
**Figure 2.10: Linearity of the Comark pressure meter (C950315) tested against a water manometer**



**Figure 2.11: Linearity of the airway pressure transducer against the Comark pressure meter (C95015).**

### **2.3.6 Calibration and linearity of flow transducer**

Prior to each measurement, a two-point calibration of the flow transducer was undertaken using a low flow rotameter (0-12 L/min Platon, Roxspur Measurement & Control Ltd, Bramley, Hants, UK). Linearity of the pneumotachograph-transducer-amplifier system was assessed by applying a range of flows to the pneumotachograph and plotting the amplified electrical output against actual flow delivered by the rotameter. The system was found to be linear (Figure 2.12)



**Figure 2.12: Linearity of the flow transducer in oxygen concentration between 21% and 100%**

### 2.3.7 Frequency response of the transducers and amplifiers

The frequency response of each transducer (airway, gastric and esophageal) and the amplifier system was tested. This was carried out by creating a quasi-instantaneous change in pressure (“pop test”) [171], e.g. by bursting a balloon whilst recording the parameter over time. The time taken for change from 10 to 90% was determined. Fourier transformation equation ( $f_{bw} = 1/(3 \times Tr)$ ) was then applied to calculate the frequency response of the system, where  $f_{bw}$  is the frequency response and  $Tr$  is the time taken for the pressure change from 10 to 90% of the final resting pressure.

The response to an instantaneous change in pressure was recorded on a laptop computer (MacBook, Apple Computer Corp, Cupertino, California, USA) using Chart software (Version 5.0, AD Instruments Pty Ltd, Bella Vista, NSW Australia) with analogue to digital sampling at 40KHz (Powerlab, AD Instruments Pty Ltd, Bella Vista, NSW Australia).

The frequency response for airway pressure measurement included the airway transducer, the connecting tubing and the amplifier. The interconnecting tubing was disconnected from the side port of the pneumotachograph and placed inside an inflated balloon. The balloon was then burst creating a quasi-instantaneous fall in pressure. The time taken for the pressure change from 10 to 90% of initial pressure ( $T_r$ ) was 15ms and the frequency response of the system calculated to be 28.8 Hz. The frequency response of the dual pressure transducer-tipped catheter and the amplifier was determined in the same manner and had a 10-90% response time of 2.8 milliseconds for the oesophageal pressure transducer and 2.2 milliseconds for the gastric pressure transducer, giving frequency responses of 71.9 Hz and 81.4 Hz respectively. Both pressure measurement systems were deemed to have adequate frequency response characteristics suitable for measurement of pressures in the study populations. In order for the measurement systems to have adequate frequency response, they should be able to measure up to four times the normal frequency of the study population. For example, since the normal respiratory rate in neonates is between 40-60 breaths per minute (Frequency of 1 hertz), the measurement systems should have a frequency characteristic of at least 4 hertz.

### 2.3.8 Measurement of the work of breathing through PTPdi

Diaphragmatic pressure time product (PTPdi) is a measure of the work of breathing that correlates with the oxygen consumption of the respiratory muscles [172]. The pressure time product of the diaphragm (PTPdi) can be calculated from the time integral of the transdiaphragmatic pressure (Pdi), where Pdi is the difference between pressures in the thoracic (pleural) and abdominal compartments, represented by esophageal (Poes) and gastric (Pgas) pressures respectively. PTPdi is the area subtended by the transdiaphragmatic pressure (Pdi) from the start of inspiration (measured at the time the flow drops to below zero) to end of inspiration (measured at the time the flow returns back to zero) (figure 2.13).

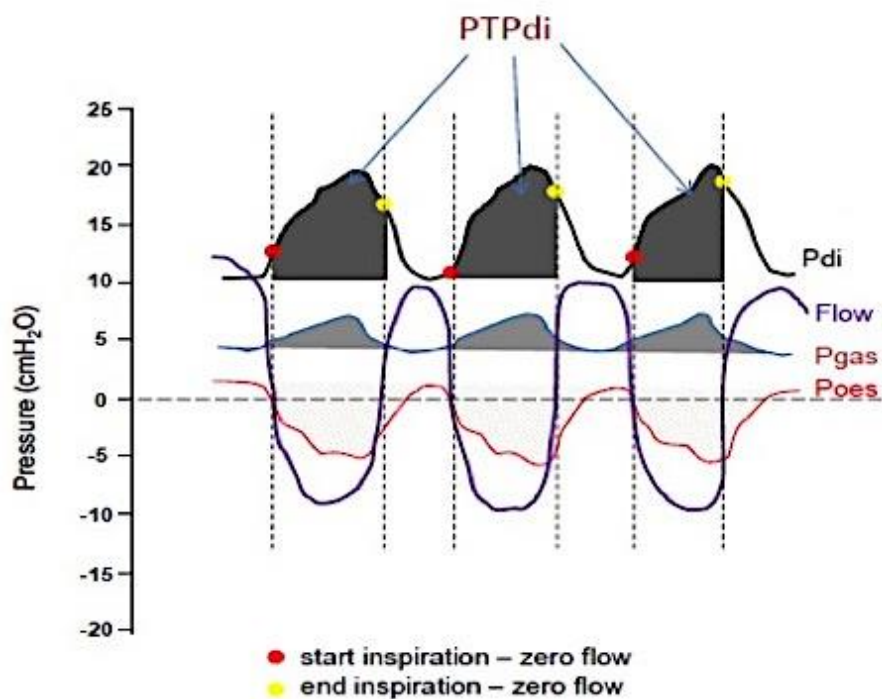


Figure 2.13: Diaphragmatic pressure time product (PTPdi) is the area subtended by Pdi from start of inspiration to the end of inspiration denoted by zero flow

### **2.3.9 Respiratory muscle strength (Pimax, Pemax and Pdimax)**

Respiratory muscle strength was assessed by measuring the maximal inspiratory (Pimax), expiratory (Pemax) and trans diaphragmatic (Pdimax) pressures during an airway occlusion sustained for at least five breaths. Pimax and Pemax were measured from the side arm of the pneumotachograph while the Pdimax was measured from a dual pressure transducer tipped catheter. Pemax and Pdimax were seen as a positive deflection in response to an occlusion while Pimax was seen as a negative deflection in response to an occlusion. Pimax, Pemax and Pdimax were defined as the single highest value generated against an occlusion.

### **2.3.10 Airway occlusion technique**

A two-way non re-breathing directional valve (Intersurgical Ltd, Berkshire, was attached to the distal end of the pneumotachograph in order to perform airway occlusions to measure muscle strength when needed. The timing of the occlusion was determined by observing the infant's spontaneous respiratory efforts such that the occlusion for Pimax was performed at end expiration and for Pemax at end inspiration. Occlusions were maintained until the infant had made at least five spontaneous breathing efforts or a maximum time of ten seconds. Three such occlusions were performed each separated by two to three minutes for the infant to settle to quiet tidal breathing. Infants were monitored throughout airway occlusion to avoid significant bradycardia (less than 100 beats per minute) or Oxygen desaturations (less than 88%).

### 2.3.11 Measurement of the tension time index

Three end-expiratory airway occlusions were performed as described in the previous section to measure the maximum inspiratory pressure (P<sub>imax</sub>) and the maximum transdiaphragmatic pressure (P<sub>dimax</sub>). In addition, airway pressure generated during the first 100ms of the first occlusion was measured to obtain P<sub>0.1</sub>, the baseline respiratory drive (Figure 2.14). The P<sub>0.1</sub> was later used in the calculation of P<sub>imean</sub>. The P<sub>imax</sub> and P<sub>dimax</sub> were defined as the largest measurements achieved from all sets of occlusions (Figure 2.14).

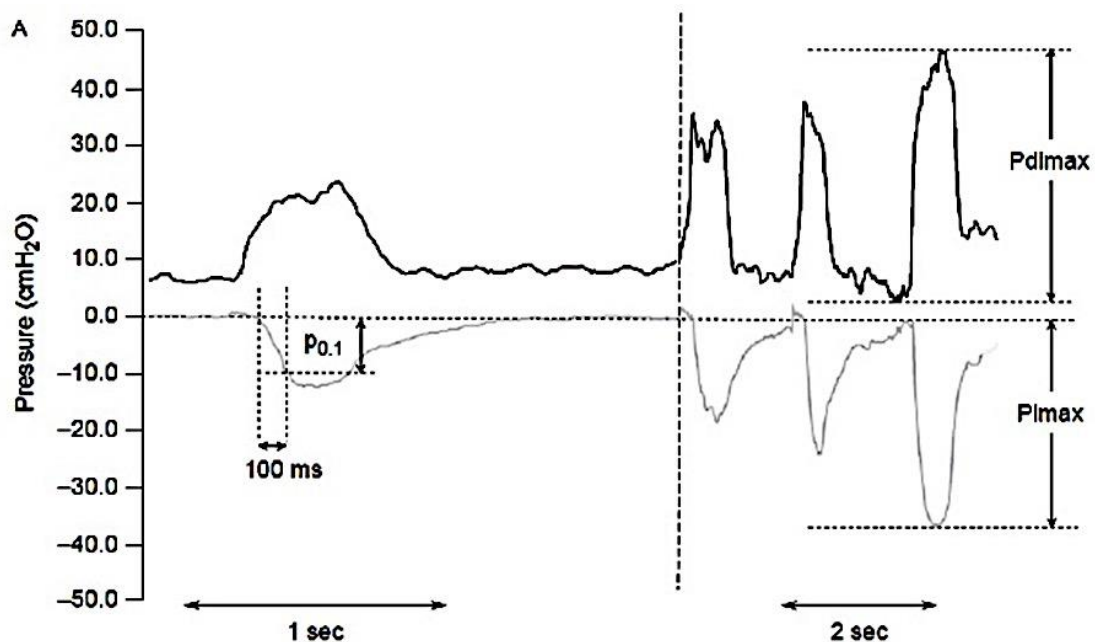
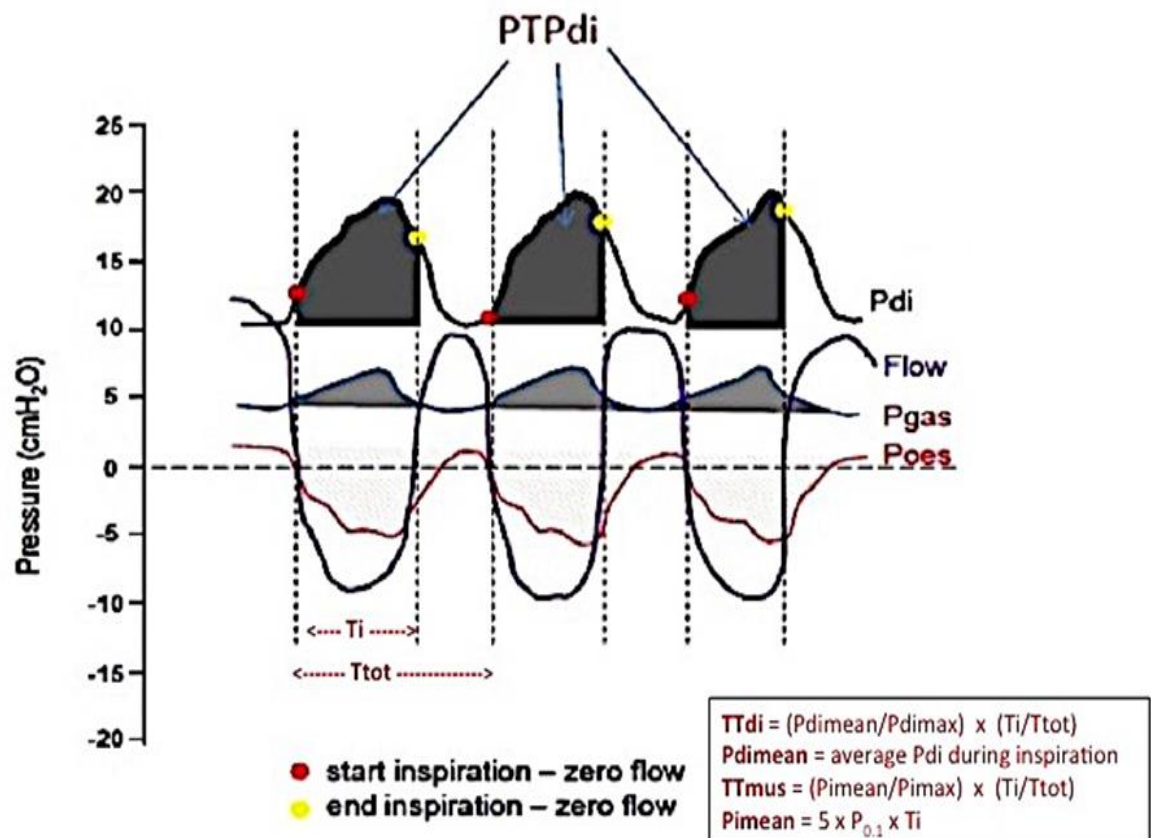


Figure 2.14: Measurement of maximum transdiaphragmatic pressure (P<sub>dimax</sub>), maximum inspiratory pressure (P<sub>imax</sub>) and the airway pressure generated during the first 100ms of each occlusion (P<sub>0.1</sub>)

The tension time index of the diaphragm (TT<sub>di</sub>) was calculated using the equation  $P_{dimean}/P_{dimax} \times T_i/T_{ot}$ . P<sub>dimean</sub> was automatically calculated by

the Labview software by averaging Pdi every 100ms during inspiration over 20 consecutive breaths. The Inspiratory time (Ti) and total respiratory cycle time (Ttot) were determined by the software from the flow trace. The tension time index of the inspiratory muscles (TTmus) was calculated using the equation  $P_{\text{mean}}/P_{\text{max}} \times T_i/T_{\text{tot}}$ . Pmean was derived from the equation  $P_{0.1} \times 5 \times T_i$  (Figure 2.15)



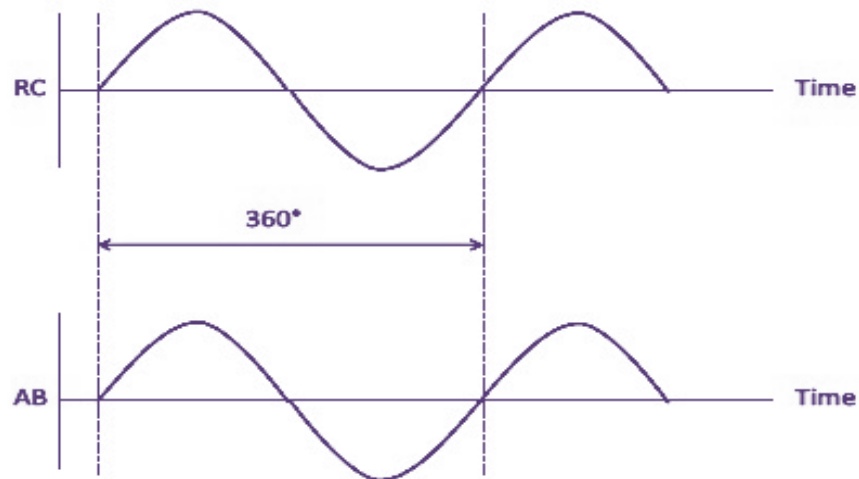
**Figure 2.15: Airway and transdiaphragmatic pressure and flow traces demonstrating; the calculation of the tension time index of the diaphragm (TTdi) and the tension time index of the respiratory muscles (TTmus), measurement of inspiratory time (Ti), total time for the breath (Ttot) and mean inspiratory transdiaphragmatic pressure (Pdimean), calculated by averaging Pdi every 100ms during inspiration during 20 consecutive breaths.**



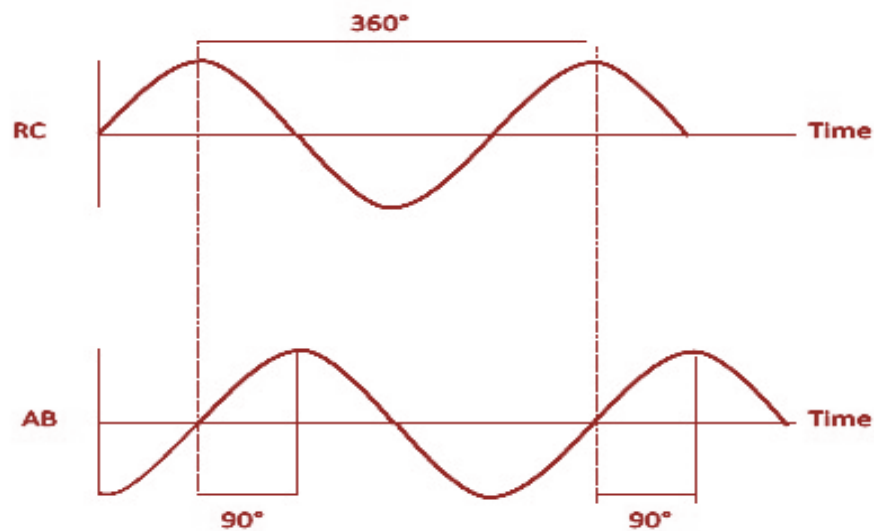
### **2.3.12 Thoraco-abdominal asynchrony**

Thoraco-abdominal synchrony was assessed using un-calibrated respiratory inductive plethysmography (RIP, Respitrace model 10.9230, Ambulatory Monitoring Inc. NY USA) in AC coupled mode. Inductance coils embedded in two elastic bandages were placed around the ribcage (at the level of the nipples) and mid-abdomen (at the level of the umbilicus) and connected to the Respitrace calibrator. Voltage signals from RIP in addition to signals from the airway pressure and flow transducers were recorded and displayed in real time on a desktop computer (OptiPlex 170L, Dell Inc, Round Rock, Texas, USA) running a custom written software application (Spectra® software version 3.0.0.9 (Grove Medical Ltd, U.K.)) with 100 Hz analogue to digital sampling (PCI-MIO-16XE-50, National Instruments, Austin TX, USA).

The inductance voltage data of ribcage and abdominal motion were analyzed by highlighting individual breaths as recorded in the Spectra software and exporting wave data to a spreadsheet (Microsoft Excel, Microsoft Corporation 2010). Individual breaths were delineated by points of zero voltage (Figure 2.16 and 2.17). A scatterplot was plotted with abdominal data points along the x-axis and ribcage data points along the y-axis to form an elliptical motion plot or “Lissajous figure” [173].



**Figure 2.16: A trace demonstrating an ideal synchronous motion of the rib cage (RC) and the abdomen (AB). A single breath is selected as a full 360-degree motion**



**Figure 2.17: A trace demonstrating an asynchronous motion of the rib cage (RC) and the abdomen (AB) wherein the RC and AB motion are out of phase by 90 degrees.**

Once the Lissajous figure was constructed, an index of asynchrony was then calculated as described Allen et al. [173] by dividing the width of the loop at mid ribcage excursion (m) by the width at the extremes of abdominal

excursion (s). Degrees of motion ( $\phi$ ) was calculated from the radian, where  $\sin \phi$  (in radians) =  $m/s$ , where  $\phi$  is  $< 90^\circ$  and where  $90^\circ < \phi < 180^\circ$ ,  $\phi = 180 - \sin [m/s]$  [173]. This was done using the Excel spreadsheet (Microsoft corporation, USA). Completely synchronous motion has a phase angle of zero degrees (figure 2.18) and paradoxical motion an angle of 180 degrees (figure 2.19) [173].

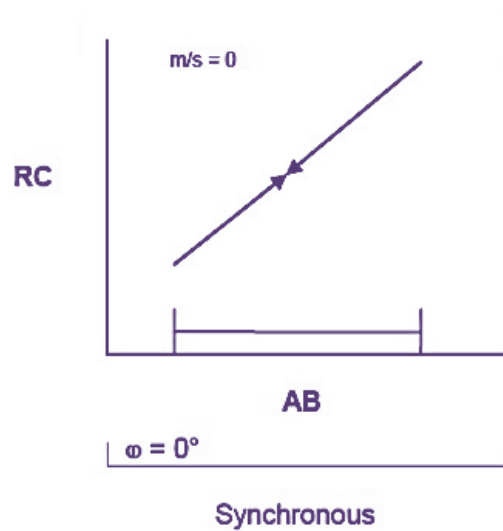
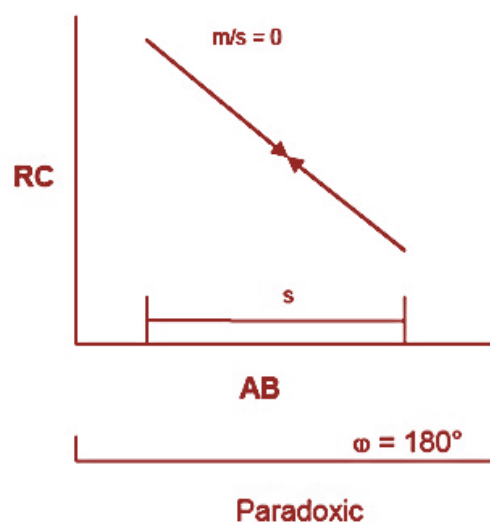
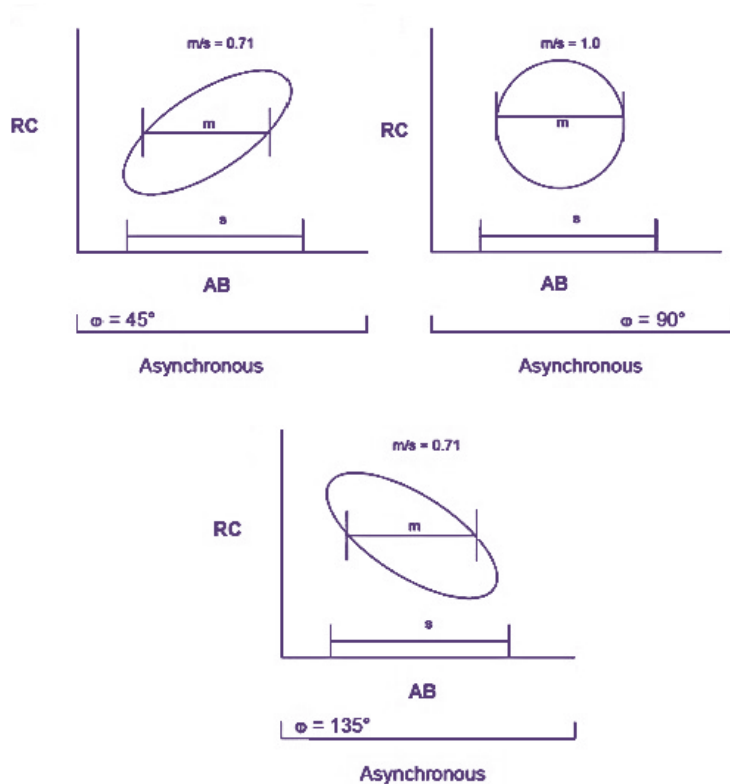


Figure 2.18: Complete synchronous motion of the rib cage and the abdomen



**Figure 2.19: Complete asynchronous motion of the rib cage and the abdomen**



**Figure 2.20: Lissajous figures demonstrating various degrees of asynchronous motion of the rib cage and the abdomen.**

Perfect ellipses as shown in the above figures (figure 2.20) assume sinusoidal breathing [173]; some infants may not breathe in a sinusoidal pattern for example infants with BPD [174]. Loops derived from non-sinusoidal waveform are non-elliptical, however even in non-elliptical traces the phase angle can still be calculated in the same way [175,176]. The margin of error associated with calculating phase angles from a non-elliptical loop has been estimated to be within 10% [173]. For each measurement five individual breaths were selected, the phase angle calculated and the result reported as the average of the five breaths.

[Figures 2.16 to 2.20: Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society. Julian L. Allen, Marla R. Wolfson, Karen McDowell, Thomas H. Shaffer. 1990. Thoracoabdominal asynchrony in infants with airflow obstruction. American Review of Respiratory Disease. Volume 141; pg 337-42. Official Journal of the American Thoracic Society].

### 2.3.13 In vitro assessment of proportional assist ventilation

For the in-vitro assessment of proportional assist ventilation (PAV), dynamic lung models were developed and used (Figure 2.21). Proportional assist ventilation was delivered using a Stephanie neonatal ventilator (Stephanie® neonatal ventilator, F. Stephan GmbH, Medizintechnik, Kirchstrasse, Germany). The dynamic lung models consisted of a commercial lung model (SLE silicon test lung, part no. N6647; SLE, South Croydon, UK) mounted inside a plastic canister (Figure 2.21).

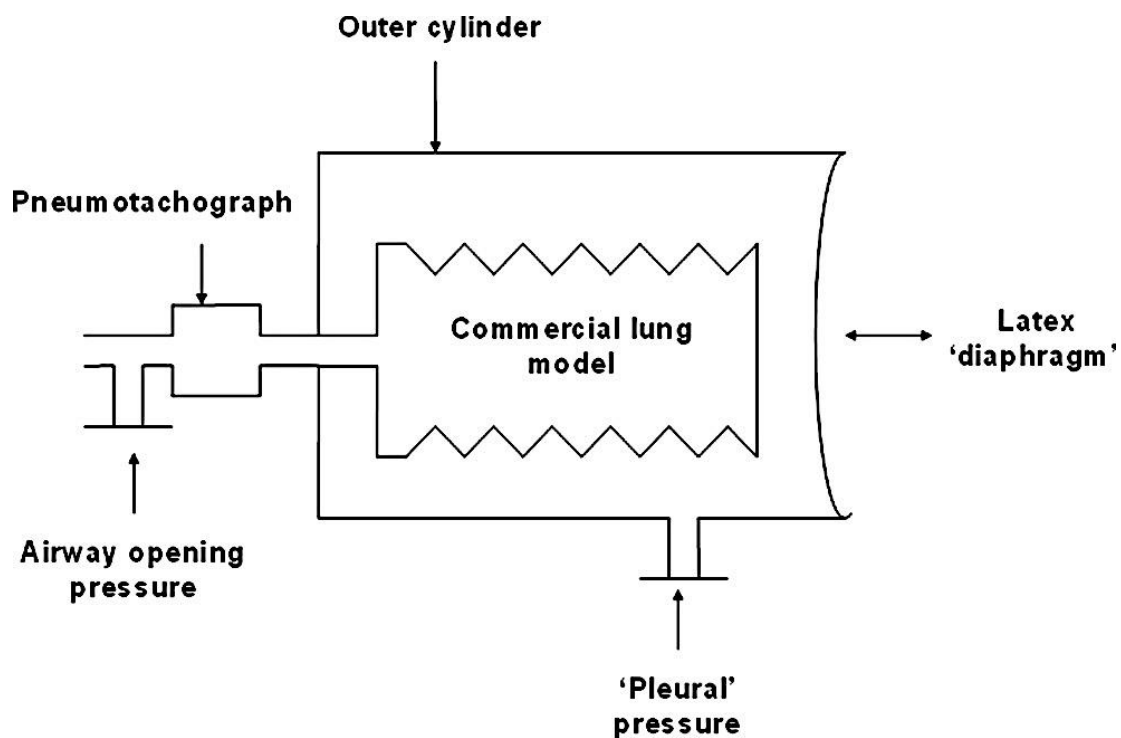


Figure 2.21: Dynamic lung model used for the in-vitro study of PAV

The outlet of the lung model was externalized through the base of the canister and attached to the ventilator circuit via a pneumotachograph. The open end of the canister was covered by a latex rubber film, which represented the 'diaphragm'. Repeated movement of the rubber film backwards and forwards simulated 'diaphragmatic' movements. The pressure changes within the cylinder, described as 'pleural pressure' (Ppl), were monitored from an outlet on the side of the canister using a pressure transducer (MP45, Validyne Corp, Northridge USA).

The dynamic lung model had a compliance of 3 ml/cm H<sub>2</sub>O and a resistance of 300 cm H<sub>2</sub>O /l/s to mimic an infant with bronchopulmonary dysplasia. A length of narrow plastic tubing between the lung model and the pneumotachograph was used to generate resistance to airflow. The resistance of the lung model was assessed using the Stephanie ventilator in Assist control (A/C) mode. The measurement of airway pressure and flow was undertaken as described in section 2.3.4.

#### **2.3.14 Blood gas analysis and calculation of oxygenation index**

Blood gas analysis was undertaken in the randomised crossover study of PAV versus ACV study using the equipment available on the NICU at King's College Hospital (ABL 700 series, Radiometer, Copenhagen, Denmark) to analyse blood pH, pCO<sub>2</sub> and pO<sub>2</sub> and to calculate the oxygenation index. The oxygenation index (OI) was calculated as follows:

$$OI = (FiO_2 \times MAP) \div PaO_2$$

- $FiO_2$ : Fraction of inspired oxygen in percentage;
- MAP: Mean airway pressure in mmHg;
- $PaO_2$ : Partial pressure of oxygen in mmHg.

A small syringe was used to draw 0.2 - 0.3 millilitres of blood from an infants' indwelling arterial line that had been inserted prior to the commencement of the study by the clinical team for clinical reasons. Only the arterial blood gases were used for the calculation of the oxygenation index. The blood gas machine was automatically calibrated four times in each 24-hour period. In addition, the blood gas analyser underwent a quality control (QC) check with the bioengineer at least once every 24 hours as per the trust and the neonatal unit protocol.

**Chapter 3:**  
**Inflation times and pressures during the resuscitation of**  
**prematurely born infants\*\***

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\*\* Work from this chapter has been submitted for publication to European Journal of Pediatrics (July 2016)



### **3.1 Introduction**

Currently, the United Kingdom Resuscitation Council recommends that during the resuscitation of prematurely born infants, for each of the initial five inflations delivered via a face mask, a peak inflation pressure of 20-25 cm H<sub>2</sub>O should be used which is sustained over two to three seconds [177]. In 2010 [178] the International Liaison Committee advised that the risk and benefits of using a peak pressure of 20-25 cm H<sub>2</sub>O sustained for two to three seconds for the first five inflations had not been evaluated [178].

Using respiratory function monitoring, our research group has demonstrated that during the resuscitation of prematurely born infants, the first five inflations were rarely maintained for more than one second, although those performing resuscitation had received appropriate training [85]. The group also demonstrated a significant positive correlation between expired tidal volumes and inflation pressures, but not inflation times [85]. Furthermore, they found no significant relationship between the inflation time and the inflation flow time [59]. Those results [59, 85] suggest that prolonging inflation time during face-mask resuscitation of prematurely born infants might not improve ventilation, whereas it might be achieved using higher pressures. Our aim, therefore, was to assess whether higher compared to lower inflation pressures and/or longer compared to shorter inflation times resulted in higher tidal volumes.

## **3.2 Methods**

### **3.2.1 Eligibility**

The study was undertaken on the delivery unit and the obstetric theatre at King's College Hospital NHS Foundation Trust, London between September 2012 and September 2014. Infants born at less than 34 weeks of gestational age requiring resuscitation at birth at King's College Hospital NHS Foundation Trust, London, UK, were eligible for entry into this study. Only infants born at or less than 34 weeks of gestational age were included in the study as such infants are more likely to require resuscitation compared to those preterm infants born at a higher gestational age. Parental written consent was only required for the analysis of the data, this was obtained when the mother was transferred to the postnatal ward. Infants with major congenital abnormalities were excluded.

### **3.2.2 Protocol**

The clinicians involved in the resuscitations had all been trained in newborn life support and had received resuscitation Council, UK NLS provider certificates. All had completed at least 6 months training on a tertiary level neonatal unit. A NM3 respiratory profile monitor (Philips Respironics, Connecticut, USA) was used, as described in section 2.2. During resuscitation the respiratory function monitor was set to display flow, expiratory tidal volume, end tidal CO<sub>2</sub> and airway pressure. Positive pressure inflations were generated by a t-piece device (Neopuff Infant resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand) attached to the face-mask. The Neopuff, a continuous flow, pressure-limiting device, had a built in manometer, a

positive end expiratory pressure (PEEP) valve and a gas flow rate of 5 l/minute. The safety pressure relief valve was set at 30 cm H<sub>2</sub>O. The clinicians were advised to follow current recommendations, that is, to use a peak inflation pressure of 20-25 cm H<sub>2</sub>O with a PEEP level of 4-5 cm H<sub>2</sub>O and to maintain the first five inflations for two to three seconds [177,178]. The peak inflation pressure was to be increased if chest wall expansion was thought inadequate. All infants were initially resuscitated with an inspired fraction of oxygen (FiO<sub>2</sub>) of 0.21. The t-piece was attached to a round face-mask (Marshall Infant, Bath, UK). The clinician, according to which mask size they felt would be most likely to achieve an adequate seal, selected a size 0 or 1 mask. Oxygen saturation monitoring was routinely used.

### **3.2.3 Outcome measures**

The infants were not randomised, but were retrospectively assigned to one of four groups according to the inflation pressure (PIP-PEEP) and inflation times they received during the first five inflations during resuscitation by face mask.

The four groups were:

- < 20 cmH<sub>2</sub>O with short inflation times (< 1.5 seconds)
- < 20 cmH<sub>2</sub>O with long inflation times ( $\geq$ 1.5 seconds)
- $\geq$  20 cmH<sub>2</sub>O with short inflation times (< 1.5 seconds)
- $\geq$  20 cmH<sub>2</sub>O with long inflation times (> 1.5 seconds)

(< 20 cm H<sub>2</sub>O lower inflation pressures;  $\geq$  20 cm H<sub>2</sub>O higher inflation pressures).

Infants who could be matched in each group for gestational age ( $\pm$  one week) and received at least 4 out of the first 5 inflation breaths according to their group characteristics were included in the analysis, unless they had made an inspiratory effort, immediately after birth and before the start of resuscitation. For example, if an infant received inflation pressures of greater than 20 and inflation times of less than 1.5 seconds for 4 breaths, then that infant was included under  $\geq 20$  cmH<sub>2</sub>O with short inflation times ( $< 1.5$  seconds) group. Infants who had less than 4 breaths in their category were excluded. Active inflations, where an infant made a spontaneous respiratory effort were excluded. From the first five passive inflations the following were analysed to determine the peak inflating (PIP) and positive end expiratory pressure (PEEP), the inflation pressure, the expiratory tidal volumes (VTe) and face mask leaks. The size of the leak was expressed as the difference between the expiratory and inspiratory volumes as a percentage of the inspiratory volume. Inflations occurring when an infant generated an inspiratory effort (active inflations) were excluded from the analysis.

#### **3.2.4 Analysis**

The data were not normally distributed and hence a non-parametric analysis was used and data presented as median (ranges). Differences across the four groups were assessed for statistical significance using the Kruskal-Wallis test. Differences between groups were assessed for statistical significance using the Mann Whitney U test. The strength of correlations was assessed using the Spearman's correlation. Analyses were undertaken using IBM SPSS statistical software (version 21)

## 3.3 Results

### 3.3.1 Demographics

A total of 18 traces were rejected: six infants were intubated immediately after birth (all the infants were less than 26 weeks of gestation), five infants could not be matched for gestational age, three infants had made a spontaneous breath prior to the first five inflations and four infants had poor quality traces. We analysed the first five passive inflations and this was determined by assessment of the flow, volume and pressure traces [85]. Sixty-four infants were included in the study, 16 in each group. There were no significant differences in the demographics of the four groups (Table 3.1).

	Lower inflation pressure short inflation time	Lower inflation pressure long inflation time	Higher inflation pressure short inflation time	Higher inflation pressure long inflation time	p value
n	16	16	16	16	
Gestational age (weeks)	30 (24-34)	30 (23-33)	31 (24-34)	31 (24-34)	0.17
Birth weight (grams)	1130 (660-2286)	1194 (645-1890)	1204 (600-2190)	1070 (600-2170)	0.64
Male gender	7 (44%)	9 (57%)	8 (50%)	9 (57%)	0.88
Antenatal steroids	14 (88%)	15 (94%)	16 (100%)	15 (94%)	0.55

Vaginal delivery	9 (57%)	11 (69%)	10 (63%)	7 (44%)	0.53
Apgar @ one minute	6 (3-8)	6 (3-7)	5 (2-8)	6 (3-8)	0.38
Apgar @ five minutes	8 (6-9)	8 (6-9)	8 (6-9)	8 (6-9)	0.17

**Table 3.1: Demographics of the four resuscitation groups.**

**Data are expressed as median (range)**

### **3.3.2 Outcomes**

At long inflation times, the expiratory tidal volumes ( $p=0.004$ ) and the percentage leak ( $p=0.02$ ) were greater at higher compared to lower pressures (Table 3.2). At short inflation times, the expiratory tidal volumes ( $p<0.001$ ) were greater and the leak was less ( $p<0.001$ ) at higher versus lower pressure. At lower pressures, the expiratory tidal volume was greater ( $p<0.001$ ) and the leak lower ( $p=0.026$ ) at a long versus a short inflation time. If, however, data from the 13 infants in whom inflations produced no measurable VTe were excluded, the significant differences disappeared. The 13 infants had a median leak of 54%, that is, within the range of the other infants. At higher pressures and long versus short inflation times, the percentage leak was greater ( $p=0.024$ ) but there was no significant difference in the expiratory tidal volumes ( $p=0.247$ )

	< 20 cmH <sub>2</sub> O, Ti ≥ 1.5 s	≥20 cmH <sub>2</sub> O, Ti ≥ 1.5 s	< 20 cmH <sub>2</sub> O Ti < 1.5 s	≥20 cmH <sub>2</sub> O Ti < 1.5 s
<b>n</b>	16	16	16	16
<b>Inflation pressure (PIP-PEEP) (cmH<sub>2</sub>O)</b>	16 (10-19)	22 (20-28)	16.5 (13-19)	22 (20-31)
<b>Inflation time (seconds)</b>	2.2 (1.5-3.8)	2.7 (1.5-4.0)	0.60 (0.3-1.3)	0.75 (0.3-1.5)
<b>Expiratory tidal volume (ml/kg)</b>	1.3 (0.09-4.0)	1.8 (0.1-7)	0.5 (0.1-6.8)	3.1 (0.2-7.1)
<b>Leak (%)</b>	30 (0-99)	59 (0-99)	52 (9-52)	15.5 (0-92)

**Table 3.2: Pressures, expiratory tidal volumes and mask leak by inflation pressure (PIP-PEEP) and inflation time group. Results are demonstrated by median (range)**

In the two groups resuscitated at lower pressures, there was a significant correlation between the expiratory tidal volumes and inflation times ( $r= 0.701$ ,  $p<0.001$ ). If, however, the infants who had no measurable expiratory tidal volumes were excluded, the correlation was no longer significant. In the two groups resuscitated with higher pressures, there was no significant correlations between the inflation times and expiratory tidal volumes ( $r= -0.098$ ,  $p=0.395$ ).

### 3.4 Discussion

This study has demonstrated that higher inflation pressures, but not longer inflation times produced significantly higher expired tidal volumes. It should be noted that the four groups did not differ significantly by gestational age or

birth weight. The effect of the higher inflation pressures was regardless of the inflation times. It should be noted, however, that face mask leak was high with prolonged inflation times, particularly at high inflation pressures. The recommendation to use a prolonged inflation time is derived from a study assessing term born newborns who had been born following elective caesarean sections under general anaesthetic [179]. Infants born by elective caesarean section have fluid filled lungs with a high viscous resistance, hence the need for a sustained inflation to improve tidal volume. Prematurely born infants, many of whom are born following spontaneous vaginal delivery will already have had some lung fluid resorption, but are likely to have stiff lungs with a short time constant. Indeed, our research group has demonstrated that despite maintenance of the inflation time for a median of 0.89 seconds the median inflation flow time was 0.11 seconds with no significant correlation with inflation flow time and the inflation time [59]. The results suggest that prolonging inflation times during the initial resuscitation of prematurely born infants is not necessary. In this study, we found low expiratory tidal volumes and large leaks were common and leaks were most common at the higher pressures with longer inflations times. On certain traces there was a high percentage of leak, but this reflects what can happen at resuscitations in the labour suite. We excluded active inflations from the analysis as we wished to assess the effects of the different pressures and inflation times per se and it is not possible to determine the magnitude of the infant's contribution during active inflations. Initial sustained inflations (SI) > 5 seconds duration have been evaluated in animal studies and human clinical trials over the last 10–15 years. However, so far there are insufficient data to recommend routine



application of SI to newborns [180].

In conclusion, higher inflation pressures were associated with significantly higher expiratory tidal volumes. A prolonged inflation time was not associated with significantly higher expiratory tidal volumes except at low inflation pressures, but in the majority of infants so resuscitated the expiratory tidal volumes were less than 2.2 ml/kg, that is, smaller than the anatomical deadspace. We, therefore, conclude that prolonging inflation time to between 1.5 and 3 seconds during resuscitation of prematurely born infants is not routinely necessary. Whether a more prolonged, that is a sustained inflation (greater than 5 seconds), would be beneficial needs further testing in randomised trials.

**Chapter 4:**  
**Randomised trial of volume targeted versus pressure-limited  
ventilation in infants born at or near term\*\***

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**\*\* Work from this chapter has been published in**  
Bhat, P., et al. (2016). "Volume-targeted versus pressure-limited ventilation in infants  
born at or near term." Eur J Pediatr **175**(1): 89-95

## **4.1 Introduction**

During volume-targeted ventilation (VTV), a relatively constant volume is delivered with each ventilator inflation regardless of changes in the infant's lung function. A meta-analysis of results of randomised controlled trials (RCTs) demonstrated that VTV compared to pressure-limited ventilation (PLV) was associated with significant reductions in death or BPD, pneumothorax, periventricular leukomalacia (PVL), grade III–IV intraventricular haemorrhage (IVH) and episodes of hypocarbia [12]. In addition, the duration of ventilation was significantly shorter in infants supported by VTV [12]. A more recently reported meta-analysis demonstrated a significant reduction in BPD [181]. None of the trials in the systematic reviews [12,181], however, included infants born at or near term, and it is, therefore, unclear whether VTV would benefit such a population.

In the RCTs [12,181], a wide range of volume target (VT) levels was used (4–10 ml/kg). Our research group has demonstrated in infants born at or near term, the level of VT influences the work of breathing (WOB) with higher levels resulting in a lower WOB [94]. Increasing the level of respiratory support by increasing the VT level, however, could unfavorably impact on respiratory muscle strength. It is also not clear whether VTV or PLV would be associated with lower thoracoabdominal asynchrony (TAA) or fewer episodes of hypocarbia in infants born at or near term. Our aim, therefore, was to undertake a randomised study of PLV and VTV in infants born at or near term to determine which modality was associated with a shorter time to extubation,

and whether this was explained by differences in the WOB, respiratory muscle strength or TAA and associated with fewer episodes of hypocarbia. This study has been presented and published [182].

## **4.2 Methods**

### **4.2.1 Eligibility**

The study was undertaken on the neonatal intensive care unit at King's College Hospital NHS Foundation Trust, London. Infants born at 34 weeks or more of gestational age who were less than 2 weeks of age were eligible for entry into the trial if they had been ventilated for less than 24 hours. Infants with congenital diaphragmatic hernia and infants who were supported by high-frequency oscillatory ventilation (HFOV) were ineligible. Infants were enrolled into the study if their parents gave informed written consent.

### **4.2.2 Protocol**

Patients were randomised using sequential opaque sealed envelopes and random number table generation to receive either VTV or PLV. The infants in both arms of the trial were supported by SLE 5000 ventilators (software versions 4.3; SLE Ltd., South Croydon, UK). All infants were ventilated via shouldered endotracheal tubes and had indwelling intra-arterial lines. The unit's standard protocol was to use PLV during acute respiratory distress that is inflation times of 0.3–0.4 s, rates of 40–60 breaths per minute (bpm) manipulated to try to achieve synchrony and peak pressures to achieve appropriate arterial carbon dioxide ( $\text{PaCO}_2$ ) levels between 4.5 and 7 kPa

providing the pH was above 7.25. The unit's standard policies were for ventilated infants regardless of ventilation mode to receive intravenous morphine if they were asynchronous with ventilator inflations and post-operatively for pain relief.

At randomisation, no changes were made to the ventilator settings of infants who were to receive PLV. For those randomised to VTV, the VT level was set at 5 ml/kg with the leak compensation at 20 %. The maximum peak inspiratory pressure (PIP) was set at 5 cmH<sub>2</sub>O above the PIP used during the previous ventilation mode to allow a volume delivery of 5 ml/kg. The PIP was increased by 1–2 cmH<sub>2</sub>O as necessary until the desired volume was delivered. During VTV with an SLE 5000 ventilator, the maximum set peak inflation was delivered to the infant only if the VT level was not achieved. Using the SLE ventilator, inflation was terminated once the VT level was achieved, which meant that the delivered inflation time might be shorter than the preset inflation time. If the delivered inflation time was noted to be less than 0.2 s, it was planned that the waveform would be altered to give a shallower upstroke to the inflating pressure to prolong the inflation time, but this was not required for any of the study population.

If infants developed a respiratory acidosis on VTV, the rate was increased in steps of 5 up to 60 bpm and, if that was not associated with resolution of the respiratory acidosis, then the VT level was increased in steps of 0.5 up to a maximum of 6 ml/kg. If infants developed a respiratory acidosis on PLV, the rate was increased in steps of 5 to a maximum of 60 bpm, and if necessary,

the pressure was increased up to a maximum of 30 cmH<sub>2</sub>O. If those manoeuvres did not bring about the desired improvement in blood gases, the infant was transferred to HFOV. Infants were deemed to have failed the randomised mode if they required HFOV or a PIP >30 cmH<sub>2</sub>O or had a pulmonary haemorrhage (diagnosed if there was fresh blood from the endotracheal tube associated with clinical deterioration).

Infants were weaned on PLV mode by first reducing the pressure to 18 cmH<sub>2</sub>O and then the rate to a minimum of 20 bpm. On VTV mode, first the tidal volume was reduced to 5 ml/kg (if a higher level had been used) and the rate to a minimum of 20 bpm. On both modes, infants were extubated when the rate had been reduced to 20 bpm. Infants were extubated into the appropriate concentration of oxygen; noninvasive respiratory support was not used. Measurements of the WOB, respiratory muscle strength and TAA were performed prior to extubation

#### **4.2.3 Outcome measures**

The primary outcome was the time from randomisation to the first successful extubation. The secondary outcome measures were the WOB, respiratory muscle strength and the thoraco-abdominal asynchrony. The clinical team, who were unaware of the research team's physiological measurement results, determined the timing of extubation. Successful extubation was defined as the infant remained extubated for at least 48 hours. Infants were reintubated according to unit's routine criteria: a major apnoea, frequent apnoeas with bradycardia or development of a severe respiratory acidosis (pH<7.20).

Physiological measurements were undertaken immediately prior to extubation. Respiratory muscle strength was assessed through the measurement of; maximum inflation (Pimax), maximum diaphragmatic (Pdimax) and maximum expiratory pressures (Pemax) generated during an airway occlusion during crying as described in section 2.3.9. The WOB was assessed over a 5-min period by measurement of the transdiaphragmatic pressure time product (PTPdi) as described in section 2.3.8. Thoracoabdominal synchrony was assessed using uncalibrated respiratory inductance plethysmography (Respirace model 10.9230, Ambulatory Monitoring, New York, USA) in AC coupled mode as described in section 2.3.12.

Oxygen saturation was monitored throughout the measurements. The clinicians caring for the infants were blinded to the results of the physiological measurements. The nurses recorded hourly the level of respiratory support on observation charts. Arterial blood gas results were also recorded on the observation charts, and from those data, the number of episodes of hypocarbia ( $\text{PaCO}_2 < 4.5 \text{ Kpa}$ ) experienced by each infant was determined. Arterial blood sampling was undertaken for clinical purposes. The infant's demographics and pre-extubation levels of respiratory support were identified from the medical records and intensive care observation charts.

#### **4.2.4 Analysis**

A convenience sample of 40 infants was recruited. Recruitment of 20 infants into each group allowed us to detect a difference of 25 % in the WOB

between the groups and differences in the results of the other physiological measurements equivalent to one standard deviation with 80 % power at the 5 % level. With regards to the statistical analysis, differences between the two groups were assessed for statistical significance using the Mann-Whitney U test or chi-square test as appropriate (IBM SPSS Version 21).

## **4.3 Results**

### **4.3.1 Demographics**

During the study period, there were 102 infants at or near term who were ventilated (Figure 4.1). The infants who were not recruited into the study were similar to those who were recruited (Table 4.1). Forty infants (19 were male) were recruited into the study (Table 4.2). Approximately half the infants had a surgical condition and were studied post-operatively (Table 4.3). The median age at randomisation did not differ between the two groups (Table 4.2).



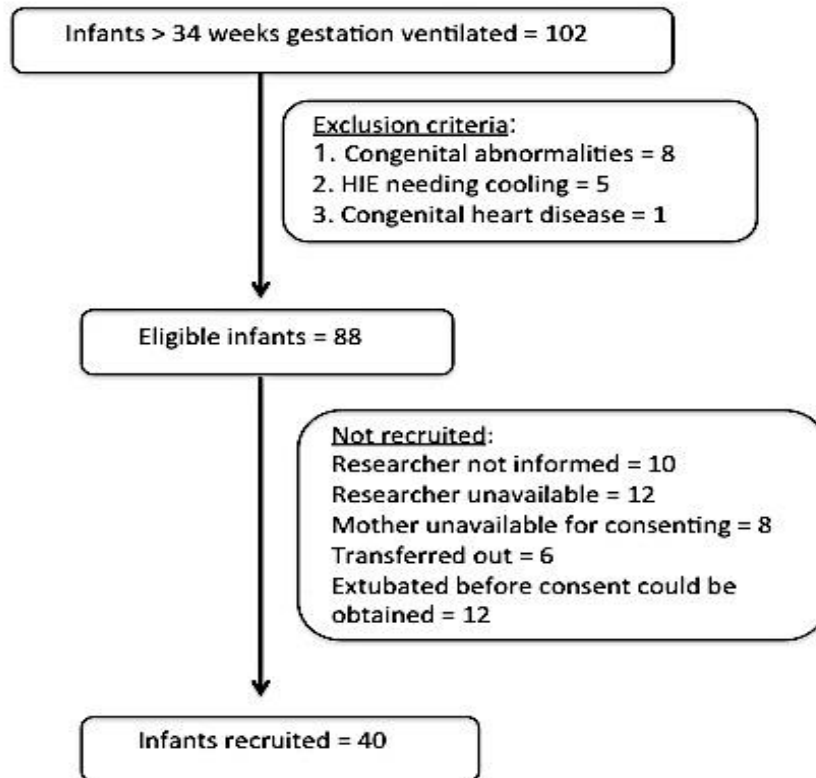


Figure 4.1: Consort diagram of recruitment

	Recruited Infants	Non-recruited Infants	p value
n=	40	62	
Gestational age (weeks)	39 (34-42)	39.5 (34-43)	0.626
Birth weight (grams)	3125 (1540-4500)	3057 (1620-4410)	0.964
Male gender	19/40 (48%)	29/62 (46%)	0.175

Table 4.1: Demographics of infants by recruitment status

	VTV	PLV
n=	20	20
Gestational age (weeks)	39 (34 – 42)	38 (34-41)
Birth weight (grams)	3362 (1540 – 4150)	2963 (1754 – 4500)
Male gender	12 (60%)	7 (35%)
Age at randomisation (days)	2 (1-13)	2 (1-13)
Received morphine	9 (45%)	11 (55%)
Pre extubation level of respiratory support		
PIP (cm H <sub>2</sub> O)	14 (9-22)	16 (12-19)
FiO <sub>2</sub>	0.21 (0.21-0.26)	0.21 (0.21-0.33)
Pre-extubation PaCO <sub>2</sub> (Kpa)	5.32 (3.83-6.1)	4.7 (3.45-5.7)

**Table 4.2: Demographics and age at randomisation by ventilation mode. Data are expressed as median (range) or n (%)**

	VTV (n=)	PLV (n=)
Gastroschisis	3	5
Sepsis	5	2
Meconium aspiration	3	3
Mild HIE	1	2
Oesophageal atresia	1	1
Congenital pneumonia	0	2
Transient tachypnea of the newborn	0	2
Intestinal obstruction	1	1
Exomphalos	1	1
Hydrops fetalis	0	1
Pelvic mass	1	0
Pneumothorax	1	0
Duodenal atresia	1	0
Spina bifida	0	1
Right sided cystic adenomatoid malformation of the lung	1	0

**Table 4.3: Diagnoses of the study population**

#### **4.3.2 Outcomes**

There were no significant differences in the pre-extubation level of respiratory support or pre-extubation PaCO<sub>2</sub> levels between the two groups (Table 4.2). The median time to extubation did not differ between the two groups being 25 (2.5–312) hours in the VTV and 33.5 (1–312) hours in the PLV group, p=0.1461 (Figure 4.2). The one infant who met failure criteria was in the VTV group and consistently required a PIP >30 cmH<sub>2</sub>O to achieve a tidal volume of 5 ml/kg.

Physiological measurements were not possible in six infants as they were extubated before the measurement could be made. In addition, no measurements were made in seven infants for technical reasons and four infants self-extubated. In some infants, only certain of the measurements could be made; for example, TAA was not attempted in infants with

gastroschisis as the bands could not be sited. There were no significant differences in the results of the physiological measurements between the two groups (Table 4.4)

	<b>VTV</b>	<b>PLV</b>	<b>p value</b>
Pimax (cm H <sub>2</sub> O)	n=12* 66.34 (16.70-115.86)	n=11* 87.11 (29.68 – 114.2)	0.260
Pemax (cm H <sub>2</sub> O)	n=12 32.88 (4.38 – 98.00)	n=10 42.05 (14.23 – 70.00)	0.674
Pdimax (cm H <sub>2</sub> O)	n=8 95.97 (51.67 – 135.77)	n=10 107.34 (31.45 – 187.90)	0.408
PTPdi	n=9 264.31 (132.15 – 329.64)	n=10 201.41 (53.62 – 493.20)	0.604
TAA (degrees)	n=6 2.35 (0.35 – 4.03)	n=8 2.40 (1.12 – 3.26)	0.950

**Table 4.4: The results of the physiological measurements by ventilation mode.  
Data are expressed as median and range**

**\*n=the number of infants in whom the measurements were made**

In the VTV group, a median of 6 (range 2–34) blood gases were obtained, and in the PLV group, a median of 9 (range 3–57) (p=0.11). In the VTV group, there was a median of 1.5 (range 0.8) episodes of hypocarbia compared to a median of 4 (range 1–13) in the PLV group (p=0.005).

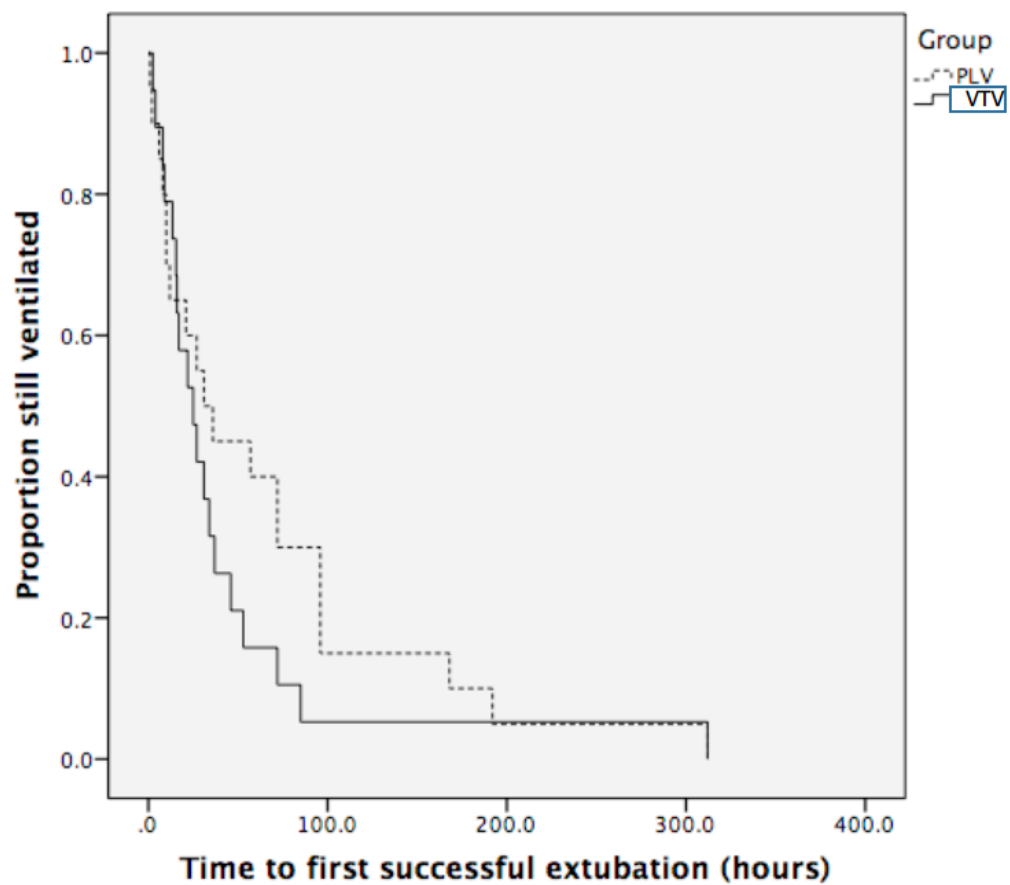


Figure 4.2: Kaplan-Meier curve for the time to randomisation to first successful extubation

#### 4.4 Discussion

This study has shown no significant differences in the time to successful extubation in at or near term-born infants supported by VTV or PLV. We recruited a convenience sample, which only allowed detection of a difference of 70 hours in the time to successful extubation between the two groups, but unexpectedly, the majority of infants were ventilated for less than that time. This perhaps reflects approximately half had surgical conditions and some were extubated very soon after the surgical intervention. In contrast, some

“surgical” infants required many days of ventilatory support, as has been our previous experience.

The study has shown no significant differences in the results of physiological measurements performed prior to extubation, but we were able only to perform the measurements in a proportion of the infants. Hence, we cannot exclude that there might have been significant differences between the two groups in the results of the physiological measurements if we had been able to study all 40 patients. In addition, we cannot exclude that physiological measurements earlier in the infants’ respiratory support career might have detected significant differences between the two groups. VTV, however, was associated with significantly fewer episodes of hypocarbia, despite the number of arterial blood gases being similar in the two groups. Indeed, there was a very high rate of hypocarbic episodes in the PLV group.

Hypocarbia is associated with PVL in prematurely born infants [183] and PVL had been reported in near term-born infants [184]. In addition, a poorer outcome has been documented in term-born infants with post-asphyxial hypoxic ischaemic encephalopathy exposed to severe hypocarbia [185,186]. Reduction in episodes of hypocarbia in at or near term-born infants then is an important outcome. This study used a VT level of 5 ml/kg as it has been shown that it is associated with a lower WOB in infants born at or near term than 4 ml/kg [94]. Use of a higher VT (6 ml/kg) resulted in a significantly lower WOB [94], but we were reluctant to use that level as it might have resulted in impaired respiratory muscle strength.

There have been a few studies examining different ventilator rates during PLV, but to our knowledge, only two included term as well as prematurely born infants. In one study [187], ventilation at a rate of 60 bpm with an inspiratory time of 0.5 s was compared to a rate of 20–40 bpm with an inspiratory time of 1 s. The number of term-born infants included in the study was not stated, but the pneumothoraces all occurred in infants of birth weight less than 1.7 kg [187]. In another study (OCTAVE) [188], rates of 60 bpm were compared to rates of 20–40 bpm, the number of term born infants was not stated. No significant difference in the pneumothorax rate was demonstrated overall.

Asynchrony can also be avoided by using patient triggered modes, but there are only two such studies, which have included term as well as preterm infants, and neither showed significant differences in air leaks. In one [189], there were no significant differences in the duration of ventilation, need for reintubation or pneumothorax or mortality rates between infants supported by synchronized intermittent mandatory ventilation (SIMV) or IMV. Only 15 infants born at term (all with meconium aspiration syndrome) were included [189]. In the other [190], 327 infants were randomised to SIMV or IMV. Ninety-three infants had a birth weight greater than 2 kg and a mean gestational age 36 weeks, and the study was adequately powered for subgroup analysis with respect to the oxygenation index and the incidence of air leaks. Amongst that subset, those supported by SIMV had a shorter duration of ventilation ( $p=0.02$ ) but had similar rates of death, oxygen dependency at 28 days and air leaks to the IMV group [190].

In conclusion, in infants born at or near term, VTV compared to PLV as implemented using the SLE ventilator did not improve the time to reach successful extubation or the results of physiological assessments. VTV, however, was associated with significantly fewer hypocarbia episodes, and hence, VTV would be recommended for its use in infants born at or near term.



## **Chapter 5:**

### **In vitro assessment of the effect of proportional assist ventilation on the work of breathing\*\***

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\*\* Work from this chapter has been published in Chowdhury, O., et al. (2016). "In vitro assessment of the effect of proportional assist ventilation on the work of breathing." Eur J Pediatr **175**(5): 639-643.

## 5.1 Introduction

During proportional assist ventilation (PAV), the ventilator can provide inflation pressure in phase with the tidal volume change to reduce the elastance load, (elastic unloading), and inflation pressure in phase with the flow change to reduce the resistance load, (resistive unloading). Unloading should then reduce the infant's work of breathing. Short-term, clinical studies of PAV in neonates so far have produced encouraging results [99,110,191,192]. However, in those studies [191,192], only elastic unloading was used; resistive unloading was not employed because in vitro studies demonstrated that oscillations appeared in the airway pressure waveform when the resistive unloading was greater than 100 cm H<sub>2</sub>O/l/s [107,111]. In the other two studies [105,192], both elastic and resistive unloading were used, but the level of resistive unloading used was only 20 cm H<sub>2</sub>O/l/s to compensate for the resistance of the infant's endotracheal tube. Thus, the clinical effectiveness of full resistive unloading has not been assessed. Indeed, the optimal level of unloading in a variety of respiratory disorders has not yet been determined and a better understanding of the effectiveness of unloading is required.

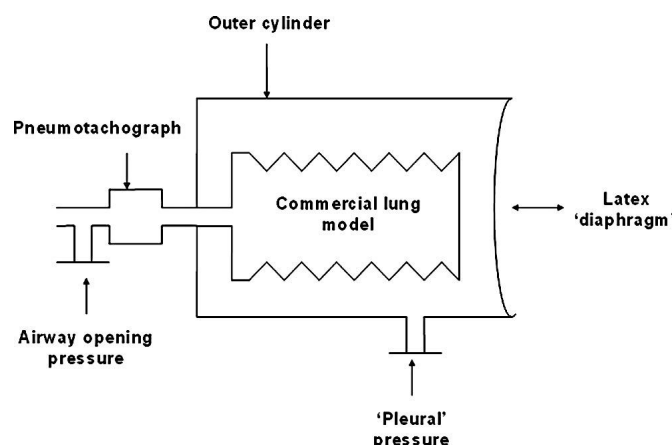
In an in-vitro study [107], using a dynamic lung model, progressive unloading led to increases in airway opening pressure and reductions in 'pleural' pressures, suggesting that unloading was reducing the 'work of breathing'. Differences in the changes in airway opening and pleural pressures, however, were demonstrated and, hence, changes in the pleural pressure may not have given an accurate estimate of the changes in the work of breathing (WOB). Hence, the magnitude of effect on the WOB could not be determined. The

aim, therefore, of this in vitro study was to measure the work of breathing directly to determine the effects of increasing resistive unloading in a model with a high resistance. The results of this study have been published as part of a study in the European Journal of Pediatrics [112].

## 5.2 Methods

### 5.2.1 Lung model and equipment

The influence of the effects of resistive unloading was examined in vitro. PAV was delivered through the Stephanie neonatal ventilator (F Stephan, Crackenback, Germany). The dynamic lung model, as described in section 2.3.13, consisted of a commercial lung model (SLE silicon test lung, part no. N6647; SLE, South Croydon, UK) mounted inside a plastic cylinder (Figure 5.1). The model had a compliance of 3 ml/cm H<sub>2</sub>O and a resistance of 300 cm H<sub>2</sub>O/l/s.



**Figure 5.1: Dynamic lung model with high resistance**

Airflow was measured by a pneumotachograph (Mercury F10L; GM

Instruments, Kilwinning, Scotland) connected to a differential pressure transducer (MP45, range  $\pm 2$  cm H<sub>2</sub>O; Validyne, Northridge, CA, USA). Tidal volume was obtained by digital integration of the flow signal. The pneumotachograph was inserted between the endotracheal tube (ETT) and ventilator manifold. Airway pressure was measured from a side port on the pneumotachograph using a differential pressure transducer (MP45, range  $\pm 100$  cm H<sub>2</sub>O; Validyne). The signals from the pressure transducers were amplified using a carrier amplifier (CD 280; Validyne). Ppl was recorded using a differential pressure transducer (MP45, range  $\pm 100$  cm H<sub>2</sub>O; Validyne). The pressure and flow signals were recorded and displayed in real time on a computer (Dell Optiplex 170L) using Spectra® software v 3.0.0.9 (Grove Medical, Hampton, UK) with 100-Hz analogue to digital sampling (PCI-MIO-16XE-50; National Instruments, Austin, Texas, USA).

### **5.2.2 Protocol**

An airway pressure limit of 25 cm H<sub>2</sub>O was used to avoid runaway pressures. A positive end expiratory pressure (PEEP) of 5 cm H<sub>2</sub>O was used. The diaphragm of the lung model was retracted manually at least ten times to simulate breathing efforts at each level of resistive unloading. The lung model had a normal compliance for an infant of 1500–2000 g, but a high resistance; hence, we selected a tidal volume of 10 ml, i.e., 6 ml/kg. The tidal volume displayed on the ventilator was used to guide the extent of the retraction of the rubber film. Baseline assessments were made with resistive unloading at zero. The measurements were repeated increasing the resistive unloading settings in increments of 25 cm H<sub>2</sub>O/l/s from zero to 200 cm H<sub>2</sub>O /l/s

(maximum resistive unloading).

### **5.2.3 Outcome measures**

A computer program (LabChart 7, AD Instruments, Dunedin, New Zealand) was used to determine the inspiratory resistive work of breathing, that is the area of the pressure volume loop below the inspiratory-expiratory line [193]. The results from five consecutive inflations at each unloading level were meaned. The effective resistance at maximum unloading was calculated by multiplying the initial resistance by the percentage reduction in the resistive WOB of the lung model at maximum resistive unloading.

### **5.2.4 Analysis**

Statistical analysis was carried out using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

## **5.3 Results**

The resistive work of breathing provided by the ventilator rose from a mean of 1.4 g·cm (SD 0.12) at a resistive unloading of 25 cm H<sub>2</sub>O/l/s to a mean of 24.2 g·cm (SD 0.56) at an unloading of 200 cm H<sub>2</sub>O/l/s. This resulted in a fall in the resistive work of breathing of the lung model from a mean of 50.2 g·cm (SD 0.14) at an unloading of 25 cm H<sub>2</sub>O/l/s to a mean of 34.2 g·cm (SD 0.22) at 200 cm H<sub>2</sub>O/l/s (Fig. 5.2). This resulted in a reduction in the effective resistance of the lung model from 300 cm H<sub>2</sub>O /l/s (at baseline) to 204 cm H<sub>2</sub>O /l/s (at maximum resistive unloading). At maximum resistive unloading, oscillations appeared in the airway pressure waveform. During resistive

unloading, the inflation pressures never exceeded 6.6 cm H<sub>2</sub>O.

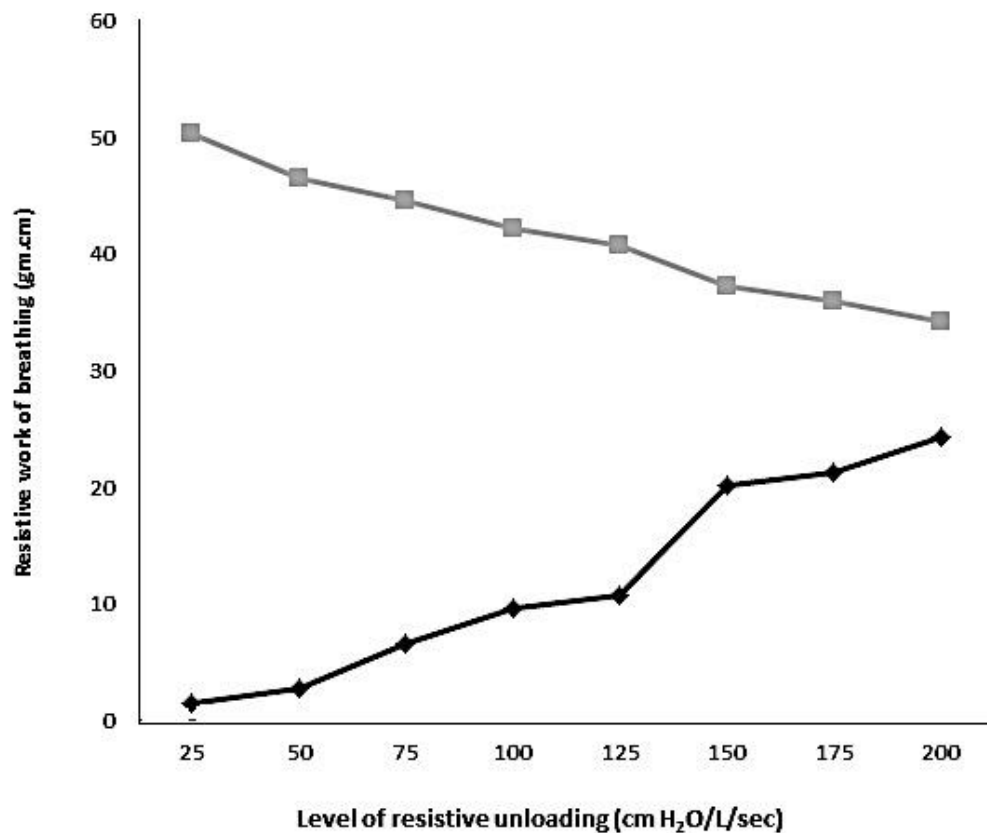


Figure 5.2: Changes in the resistance work of breathing in the high-resistance lung model with increasing levels of resistive unloading. WOB: *square*, lung model; *diamond*, ventilator

## 5.4 Discussion

Although the resistive unloading did reduce the resistive workload in the lung model, the reduction in effective resistance was small with a reduction in the resistance of the lung model from 300 cm H<sub>2</sub>O/l/s (at baseline) to 204 cm H<sub>2</sub>O/l/s (at maximum resistive unloading 200 cm H<sub>2</sub>O/l/s). This relative ineffectiveness is likely explained by the low pressures generated during resistive unloading event at the maximum unloading of 200 cm H<sub>2</sub>O/ l/s (6.6 cm H<sub>2</sub>O). Resistive unloading might be more effective if higher unloading

levels could be used, but oscillations in the airway pressure waveforms were demonstrated in both in vitro [107,112] and in vivo [105] models at higher levels of unloading. Indeed, we noted airway pressure oscillations at an unloading level of 200 cm H<sub>2</sub>O/l/s and thus would not recommend higher levels of resistive unloading as currently delivered.

In our in vitro model, there was no leak in the system. Infants, however, are frequently ventilated by straight endotracheal tubes, and there is often a leak, which can be variable. During unloading, inflation pressure is delivered in proportion to the change in volume or flow during inspiration; in the presence of a large leak, this may be inaccurate. Our results are pertinent to clinical practice as they demonstrate what will happen when there is minimal or no leak around the endotracheal tube. The resistive WOB was not corrected for the tidal volume, as this would not be appropriate as resistive WOB is determined by flow rather than tidal volume and flow is a continuous variable. Although our model was able to replicate the increased resistance noted clinically in infants with BPD, the model was not constructed to simulate varying lung inhomogeneity.

In conclusion, resistive unloading was relatively ineffective and hence as currently delivered is unlikely to be of clinical benefit to infants with a high resistance load.

## **Chapter 6:**

### **Randomised crossover study of proportional assist versus assist control ventilation\*\***

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**Bhat, P.**, et al. (2015). "Crossover study of proportional assist versus assist control ventilation." Arch Dis Child Fetal Neonatal Ed 100(1): F35-38.



## **6.1. Introduction**

Proportional assist ventilation (PAV) is a new mode of ventilation during which the applied pressure is servo controlled, based on continuous input from the infant throughout each spontaneous breath. In addition, the ventilator can provide inflation pressure in phase with the tidal volume change in order to reduce the compliance load (ie, the load due to the stiffness of infant's lungs) and in phase with the flow change to reduce the resistance load (ie, the load due airflow obstruction), termed elastic and resistive unloading, respectively [106]. The clinician can set the level of unloading, which should potentially decrease the infant's work of breathing. Unloading might be particularly helpful in very prematurely born infants ventilated beyond the first week after birth; as such infants are at high risk of developing BPD and can have severe lung function abnormalities.

In a randomised crossover comparison of PAV and patient triggered ventilation (assist control ventilation (ACV) or synchronised intermittent mandatory ventilation (SIMV)) which included 22 ventilator dependent infants with evolving BPD, gas exchange was successfully maintained at significantly lower mean and peak pressures on PAV [110]. A limitation of that study was that two different ventilators (the Stephanie (Fritz Stephan GmbH) for PAV and the BabyLog 8000 (Draeger) for ACV and SIMV) were used which might have influenced the results. PAV has been shown to reduce thoracoabdominal asynchrony (TAA) compared with support by continuous positive airways pressure in prematurely born infants [194]. Reduction in TAA might improve oxygenation. Lower levels of asynchrony might also reduce the

likelihood of respiratory muscle fatigue and infants then might have better respiratory muscle strength on PAV. The aim of our study was, therefore, to test the hypothesis that the work of breathing and ventilator infant asynchrony would be lower and respiratory muscle strength would be better and hence there would be improved oxygenation after a one hour period on PAV compared with after a one hour period on ACV in prematurely born infants with evolving BPD remaining ventilator dependent after the first week after birth. This study has been presented and published [191]

## **6.2. Methods**

### **6.2.1 Eligibility**

The study was undertaken on the neonatal intensive care unit at King's College Hospital NHS Foundation Trust, London. Prematurely born infants remaining ventilated after the first week after birth were eligible for entry into this study if they were being supported by ACV. Infants were entered into the study if their parents gave informed written consent. Infants with major congenital abnormalities neuromuscular disorders, moderate to severe congenital heart disease, chromosomal disorders and those receiving neuromuscular blockade were excluded from the study.

### **6.2.2 Protocol**

In the neonatal unit at King's College Hospital, London, it was routine practice for infants needing mechanical ventilation to be supported by the SLE 5000 ventilator. For the purposes of this study, the infants were transferred from the SLE 5000 ventilator to ACV on the Stephanie ventilator using the same

ventilator settings (baseline). All infants as per the unit's routine policy were ventilated via shouldered endotracheal tubes. One hour was allowed for stabilisation of the infant on the Stephanie ventilator. A blood gas analysis was then performed and the baseline ventilator settings were noted. During the stabilisation period, compliance and resistance settings were noted every 10 min when the infant was not obviously fighting the ventilator and the mean of the six results taken. The infant was then randomised to receive first either PAV or ACV mode each for one hour and for the second hour the alternative mode.

During ACV mode, the peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP) and the inflation time were kept the same as at baseline. The backup rate was set at 40 breaths per minute. During PAV, the maximum PIP was set at 5 cm H<sub>2</sub>O above the PIP on ACV, as recommended by Schulze et al [109]. The PEEP level during PAV was the same as at baseline and the PEEP and the inflation time during back up ventilation was the same as at baseline. Whenever cessation of spontaneous breathing occurred for more than 5 s during PAV, the ventilator automatically delivered mandatory backup inflations until the infant made a spontaneous breath. Elastic unloading, which was used only during inspiration, was initially set at 75% of full unloading; full unloading was the level of unloading which increased the infant's compliance to the expected 'normal', that is, 2.0 mL/cm H<sub>2</sub>O. If after 10 min the infant remained stable and no airway pressure waveform abnormalities were observed, the unloading was increased to 100%. If airway pressure waveform abnormalities were then noted [110], the

unloading was reduced back to 75%. Although the infants currently studied were all ventilator dependent beyond 1 week after birth, their respiratory system resistances were not found, on average, to be very high; the median respiratory system resistance was 86.5 (range 85–174) cm H<sub>2</sub>O/L/s. We have previously demonstrated that the likelihood of oscillations appearing in the airway pressure waveform was greater when elastic unloading was used in a low compared with a high resistance model [107]. In addition, in the in vitro model [107], oscillations in the airway pressure waveform appeared when the resistive unloading was greater than 100 cm H<sub>2</sub>O/L/s. Hence, in this study, we decided not to use resistive unloading. During the last 5 minutes on each mode, the work of breathing, the level of asynchrony, respiratory muscle strength and blood gases were measured.

### **6.2.3 Outcome measures**

The work of breathing was assessed by measurement of the transdiaphragmatic pressure time product (PTP<sub>di</sub>). Transdiaphragmatic pressure (P<sub>di</sub>) was obtained from measurements of oesophageal (P<sub>oes</sub>) and gastric (P<sub>gas</sub>) pressures, measured using a dual-pressure transducer tipped catheter and associated amplifier (Gaeltec, Dunvegan, UK). The catheter was inserted and positioned as described in section 2.3. Airflow was measured using a pneumotachograph (Mercury F10L; GM Instruments, Kilwinning, UK) connected to a differential pressure transducer (MP45; Validyne Corporation, Northridge, California, USA). The pneumotachograph was positioned between the endotracheal tube and the ventilator manifold. Airway pressure was measured from a side port on the pneumotachograph using a second

differential pressure transducer (MP45; Validyne Corporation). The signals from the flow and airway pressure transducers were amplified using a carrier amplifier (CD280; Validyne Corporation). The pressure and flow signals were recorded and displayed in real time on a computer (Dell Optiplex 170L) running an application written with Labview software (National Instruments, Austin, Texas, USA) with 100 Hz analogue-to-digital sampling (PCI-MIO-16XE-50, National Instruments).

Transdiaphragmatic pressure was calculated by the digital subtraction of Poes from Pgas by the acquisition software. The PTPdi was obtained by integration of Pdi with time for each breath and expressed per minute. The beginning and the end of the inspiratory phase of each breath were determined from the phase transition of the flow signal (figure 2.13). The mean PTPdi was calculated from the first set of 20 consecutive breaths without artefact during the last 5 min of each hour on ACV and PAV modes.

Respiratory muscle strength was assessed by performing airway occlusions, as described in section 2.3.10, to obtain the maximum inspiratory (Pimax), maximum expiratory (Pemax) and maximum transdiaphragmatic (Pdimax) pressures. Airway occlusions were maintained for five to seven breaths and three sets of occlusions were performed. Sufficient time was allowed between occlusions for the infant to settle to quiet tidal breathing. The airway occlusion was discontinued if a pronounced desaturation ( $< 88\%$  for  $> 5$  seconds) or bradycardia ( $< 100$  beats per minute) occurred. A two-way non-breathing valve attached to the distal end of the pneumotachograph was used whilst performing the occlusion. The maximum pressures achieved from the series

of occlusions were recorded.

TAA was assessed by respiratory inductance plethysmography (Ambulatory Monitoring Inc, Ardsley, New York, USA), as described in section 2.3.12. The rib cage band was placed at the level of the nipples and the abdominal band was placed at the level of the umbilicus or midway between the bottom of the rib cage and the iliac crest. The signals were recorded and displayed in real time on a computer (Dell Optiplex 170L) running Spectra software (3.0.1.4) (Grove Medical, London, UK). From the recorded traces of the rib cage and abdominal wall motion, 10 consecutive artefact free breaths were selected and a Lissajous figure constructed. The phase angle  $\phi$  was calculated as an index of TAA. A  $0^\circ$  phase angle represents synchronous motion of the ribcage and abdomen while a  $180^\circ$  phase angle represents completely out-of-phase or paradoxical motion between rib cage and abdomen.

The number of desaturations (desaturation defined as an oxygen saturation less than 88%) on each mode was noted. An arterial blood sample from an indwelling catheter was obtained at the end of each hour, the ventilatory settings were noted and the oxygenation index (OI) was calculated.

#### **6.2.4 Analysis**

The planned sample size was 18 infants to allow detection between the two ventilator modes of a difference equivalent to 0.7 SD in the results of the physiological measurements with 80% power and two-sided significance of 5%. The differences in the results between the two modes were analysed with

the Wilcoxon signed rank test using IBM SPSS statistical software, V.21 (IBM Corporation, USA).

## **6.3. Results**

### **6.3.1 Demographics**

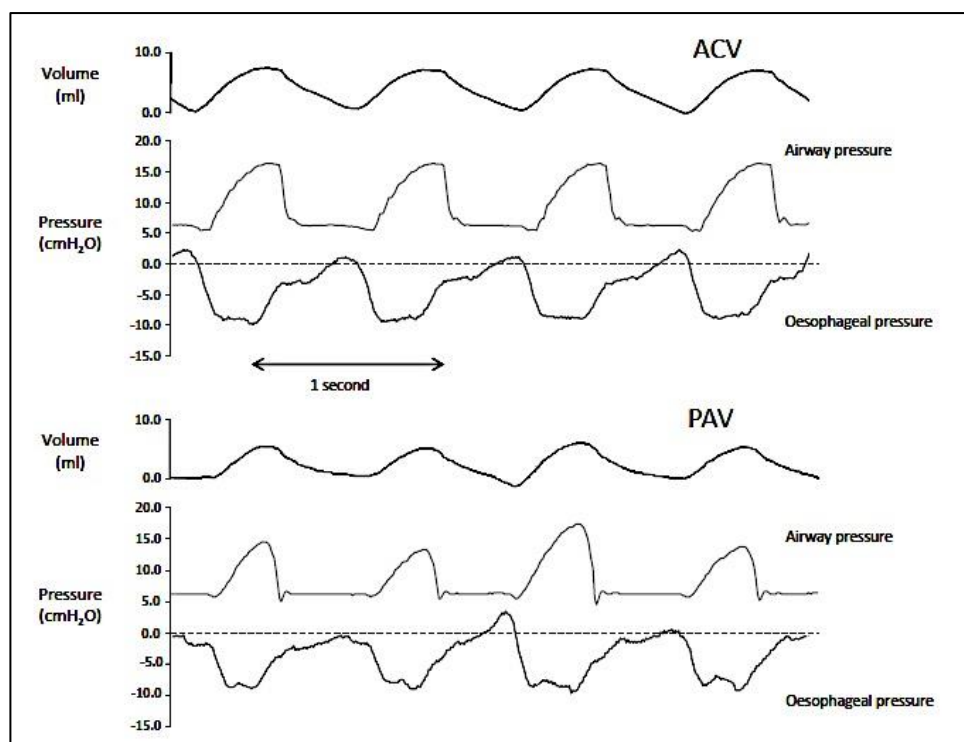
Recruitment to the trial was stopped at 12 patients since it emerged at that point that the OI results were in favour of PAV for all 12 patients. The decision was taken by the clinical team and the trial statistician in the knowledge that the probability of 12/12 results in the same direction (here favoring PAV), if both modes were in fact equally effective, was extremely small at 0.0002 ( $0.5^{10}$ ). In addition, although there were no apparent adverse effects, certain of the physiological measurements are invasive and/or require airway occlusions. Hence, it was unanimously agreed that it was both inappropriate and unnecessary to continue the trial further since the hypothesis had been conclusively answered.

The attained sample of 12 infants allowed the detection of a difference of 0.9 SDs with 80% power and two-sided significance of 5%. The 12 infants (seven boys) had a median gestational age of 25 (range 24–26) weeks, birth weight of 721 (range 535–930) grams and baseline inspired oxygen fraction ( $\text{FiO}_2$ ) of 0.50 (range 0.45–0.70) and were studied at a median age of 43 (range 8–86) days, when they had a median weight of 990 (range 598–1530) grams. Their median baseline compliance was 0.6 (range 0.3–0.9) mL/cm  $\text{H}_2\text{O}$ . No waveform abnormalities were noted in any of the 12 infants when studied at 75% elastic unloading. At 100% unloading two infants had desaturations,

although no waveform abnormalities. They were, therefore, returned to 75% of unloading at which level they remained throughout the rest of the PAV study period without waveform abnormalities appearing or further desaturations.

### 6.3.2 Outcomes

Five of the 12 infants were studied first on PAV. With regards to the results of the 12 infants studied, overall, after 1 h on PAV, the median mean airway pressure was significantly lower than after 1 h on ACV (8.4 (range 7–9) cm H<sub>2</sub>O vs 9.1 (range 7–11) cm H<sub>2</sub>O, respectively,  $p=0.028$ ). In addition, on PAV the peak inflation pressures (17 (range 13–20) cm H<sub>2</sub>O vs 18 (range 14–20) cm H<sub>2</sub>O,  $p=0.036$ ) were significantly lower (figure 6.1).



**Figure 6.1: Volume, airway and oesophageal pressures on assist control ventilation (ACV) and proportional assist ventilation (PAV). The airway pressure varies according to oesophageal pressure during PAV, but not ACV**



	PAV	ACV	P value*
Mean airway pressure (cm H <sub>2</sub> O)	8.4 (7.1 - 9.0)	9.1 (7.1 - 11.0)	0.028
Peak Inspiratory pressure (PIP) (cm H <sub>2</sub> O)	17 (13 - 20)	18 (14 - 20)	0.036
Expired tidal volume (mls/kg)	6.8 (3.7-7.4)	7.2 (2.7 - 7.8)	0.182
Respiratory rate (breaths/min)	54 (40 - 66)	57 (46 - 74)	0.025
SaO <sub>2</sub> (%)	96 (93 - 98)	93 (92 - 98)	0.021
FiO <sub>2</sub>	0.40 (0.21-0.50)	0.50 (0.30-0.60)	0.005
PaCO <sub>2</sub> (kpa)	7.6 (5.7 - 10.0)	7.6 (5.7 -12.1)	0.814
PaO <sub>2</sub> (kpa)	7.2 (4.4 - 13.2)	6.1 (3.9 -11.7)	0.158
PTPdi (cm H <sub>2</sub> O.s/min)	217 (60 - 556)	309 (55 - 544)	0.005
Oxygenation index	5.6 (5.0 - 10.7)	10.1 (7 - 16.1)	0.002
Pimax (cm H <sub>2</sub> O)	21.9 (11.2 - 37.3)	23.5 (13.6 - 38.6)	0.182
Pemax (cm H <sub>2</sub> O)	25.7 (6.5 - 42.7)	15.9 (3.0 - 35.7)	0.010
Pdimax (cm H <sub>2</sub> O)	44.3 (21.3- 66.5)	37.9 (19.5- 45.2)	0.002
TAA (degrees)	1.2 (0.4 - 3.5)	1.9 (1.2 - 3.3)	0.050
Desaturation episodes (n)	1 (0-3)	1 (0-5)	0.200

**Table 6.1: Comparison of airway pressures, physiological outcomes and blood gas exchange by ventilator mode. The results are expressed as the median (range). ACV, assist control ventilation; PAV, proportional assist ventilation; TAA, thoracoabdominal asynchrony.**

After 1 h on PAV compared with 1 h on ACV, the PTPdi levels were lower ( $p=0.005$ ) and Pdimax levels ( $p=0.002$ ) and Pemax levels ( $p=0.010$ ) were higher (table 6.1). The median OI following 1 h on PAV was significantly lower than that following 1 h on ACV ( $p=0.002$ ). There were no significant differences in the PaCO<sub>2</sub> levels between the two modes ( $p=0.814$ ) and the number of desaturation episodes was similar ( $p=0.20$ ).

## **6.4 Discussion**

This study has demonstrated that PAV compared with ACV in prematurely born infants ventilated beyond the first week after birth resulted in a reduced work of breathing and a lower OI. The lower OI is in keeping with the findings of Schulze and colleagues [110] that despite a reduced mean airway pressure on PAV compared with ACV/SIMV, the inspired oxygen level and pulse Oximetry readings were not significantly different on the two modes in very prematurely born infants (mean gestational age 25.6 weeks) with evolving chronic lung disease. In addition, in prematurely born infants with acute respiratory distress (birth weights between 600 and 1200 g) on 45-min epochs on PAV compared with 45-min epochs on ACV or intermittent mandatory ventilation, similar arterial oxygenation was maintained despite lower airway and trans pulmonary pressures during PAV [99]. The lower mean airway pressure and lower OI that this study has demonstrated on PAV likely reflect that during PAV the applied pressure is servo controlled throughout each spontaneous breath, whereas during ACV, synchronization of inflation is only

at the beginning of inspiration. In addition, the lower OI might also reflect the reduced level of asynchrony during PAV, which was not statistically significant ( $p=0.05$ ).

High airway pressures and airway pressure oscillations have been demonstrated when excessive amounts of elastic and resistive unloading are used [109]. High airway pressures can be prevented by the use of a set limit on the maximum peak inflation pressure, provided care is taken to ensure this does not result in very short inflation times [111]. In this study, a maximum peak inflation pressure was set as has been recommended [110] and no airway pressure waveform abnormalities were experienced despite using up to 100% elastic unloading. Our results may also reflect we used only elastic unloading and not resistive unloading. The compliance used to determine the amount of unloading was taken from the ventilator display when the infants were supported by ACV during the stabilisation period. As they were able to make spontaneous efforts, it is possible the ventilator display gave an overestimate of compliance and we were not fully unloading them

In conclusion, this study has demonstrated that 1 hour on PAV compared with 1 hour on ACV results in a significant improvement in the OI and a reduction in the work of breathing.

## **Chapter 7:**

### **Prediction of extubation outcome using the tension-time index\*\***

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**Bhat, P.**, et al. (2016). "Prediction of infant extubation outcomes using the tension-time index." Arch Dis Child Fetal Neonatal Ed **101**(5): F444-447.

## **7.1 Introduction**

The tension-time index of the diaphragm (TTdi) is a composite assessment of the load on and the capacity of the diaphragm. TTmus is a non-invasive tension-time index of the respiratory muscles. A pilot study done in neonates [126], where data from 20 infants were retrospectively analysed using previously describe cut-offs (TTdi > 0.15 and TTmus of > 0.18), showed that there were significant differences in TTdi and TTmus between those who were and were not successfully extubated. Additionally, a TTdi below 0.15 and TTmus below 0.18 were similarly accurate in predicting successful extubation in infants with 100% specificity and sensitivity. This study, however, was not adequately powered and measurements were taken as part of an on-going randomised trial. Therefore, the aim of our study was to test the hypothesis that TTdi of greater than 0.15 and TTmus of greater than 0.18, predicted extubation failure and that they performed better than respiratory muscle strength (Pimax, Pdimax), respiratory drive (P0.1) and work of breathing (transdiaphragmatic pressure-time product (PTPdi)) or routinely available clinical data. The results of this study have been presented and published [195]

## **7.2 Methods**

### **7.2.1 Eligibility**

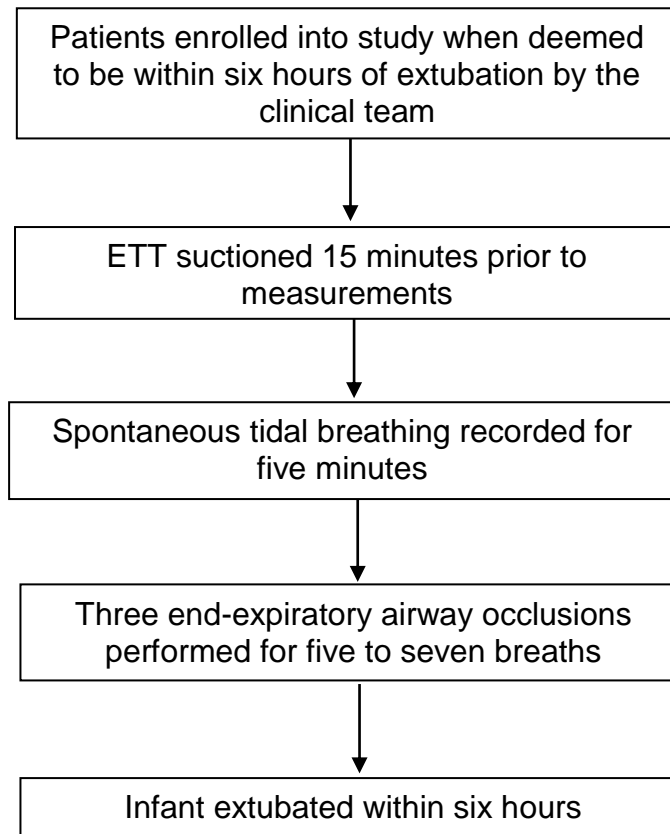
The study was undertaken on the neonatal unit at King's College Hospital NHS Foundation Trust, London. Ventilated infants born at term or prematurely deemed ready to be extubated in the next six hours were included in the

study. Written informed consent was obtained from parents prior to the commencement of the study. Infants with major congenital abnormalities were excluded.

### **7.2.2 Protocol (figure 7.1)**

All infants followed the unit's routine weaning policy. It was the unit policy that once the decision to extubate within the next six hours was made, all sedation was stopped and, in infants of less than 34 weeks of gestational age, caffeine was administered. All infants were ventilated via shouldered endotracheal tubes as per the unit policy. All measurements were performed with the patient supine and with stable blood gases in the following ranges: pH 7.35–7.45, PaCO<sub>2</sub> 5–7 kPa, PaO<sub>2</sub> 7–10 kPa. The endotracheal tube was suctioned 15 minutes prior to measurements. The clinical team, who were blinded to the results of the physiological assessments, made the decision to extubate and reintubate. The infants were then extubated to CPAP or high flow nasal cannula or low flow nasal cannula oxygen or to room air as per unit guidelines.

Extubation failure was defined as the need for reintubation within 48 hours of extubation. The criteria for reintubation were a major apnoea, frequent apnoeas with bradycardia, a severe respiratory acidosis (pH <7.20) or failure to improve despite instituting CPAP. The nurses recorded hourly on observation charts, the level of respiratory support required by the infant. From those charts, the peak inflation pressure (PIP) and the fraction of inspired oxygen (FiO<sub>2</sub>) immediately before extubation were obtained.



**Figure 7.1 Overview of the tension time index study protocol**

### **7.2.3 Outcome measures**

To measure TTdi, oesophageal (Poes) and gastric (Pgas) pressures were measured using a dual pressure transducer tipped catheter and associated amplifier (Gaeltec, Dunvegan, UK). The catheter was inserted through the nostril and positioned as described in section 2.3.2. Transdiaphragmatic pressure (Pdi) was then calculated by digital subtraction of the oesophageal from the gastric pressure. Flow was measured using a pneumotachograph

(Mercury F10L; GM Instruments, Kilwinning, UK) connected to a differential pressure transducer (MP45; Validyne, Northridge, California, USA). The pneumotachograph was placed between the endotracheal tube and ventilator manifold. Airway pressure was measured from a side port on the pneumotachograph using a differential pressure transducer (MP45). The flow and airway pressure signals were amplified (CD280; Validyne) and recorded and displayed in real-time on a computer (Dell Optiplex 170L) running an application written with Labview software (National Instruments, Austin, Texas, USA) with 100 Hz analogue to digital sampling (PCI-MIO-16XE-50).

Once the dual pressure catheter and the pneumotachograph were in place, five minutes of spontaneous tidal breathing was recorded. The first twenty consecutive breaths recorded without electrical interference or double breaths and with the infant breathing calmly were analysed, from which the inspiratory time ( $T_i$ ), total time for each breath ( $T_{tot}$ ), and mean transdiaphragmatic pressure ( $P_{dmean}$ ) were determined and mean of the 20 breaths recorded.  $T_i$  and  $T_{tot}$  were measured from the respiratory flow trace and the Labview software automatically calculated  $T_i/T_{tot}$ .

End-expiratory airway occlusions were then performed, as described in section 2.3.10, to measure the maximal inspiratory ( $P_{imax}$ ) and maximal transdiaphragmatic ( $P_{dimax}$ ) pressures and the airway pressure generated during the first 100 ms of the first inspiratory effort of each occlusion ( $P_{0.1}$ ) (figure 2.14).  $P_{imax}$  and  $P_{dimax}$  were the maximum airway or transdiaphragmatic pressures, respectively, generated during the sets of



occlusions. Following measurement of P<sub>imax</sub>, P<sub>dimax</sub> and P<sub>0.1</sub>, the infant was returned to mechanical ventilation and extubated once stabilized within the next six hours. The transdiaphragmatic pressure-time product (PTP<sub>di</sub>) was calculated by the integration of the transdiaphragmatic pressure signal with time for each breath and expressed per minute (figure 2.13). The beginning and the end of the inspiratory phase of each breath were determined from the phase transition of the flow signal (figure 2.13).

TT<sub>di</sub> was calculated using the equation  $(P_{di\text{mean}}/P_{di\text{max}}) \times (T_i/T_{\text{tot}})$ . P<sub>di</sub>mean was obtained by averaging P<sub>di</sub> every 100 ms during inspiration, as indicated by the respiratory flow trace. The inspiratory time (T<sub>i</sub>) and the total time for the breath (T<sub>tot</sub>) were measured from the respiratory flow trace (figure 2.25). TT<sub>mus</sub> was calculated using the equation  $(P_{i\text{mean}}/P_{i\text{max}}) \times (T_i/T_{\text{tot}})$ , where the mean inspiratory airway pressure (P<sub>i</sub>mean) was obtained from the formula  $5 \times P_{0.1} \times T_i$ . Both TT<sub>di</sub> and TT<sub>mus</sub> were calculated as the mean of 20 consecutive artefact free breaths. Cut-offs of TT<sub>di</sub>  $\geq 0.15$  and TT<sub>mus</sub>  $\geq 0.18$  were used as previously described.

#### **7.2.4 Analysis**

The sample size for the study was calculated as follows: In a prespecified sample size of 60, it was expected that 25% of babies would fail extubation. Hence, the sensitivity of the cut-offs previously identified [126,158] would be estimated with a 95% CI $\pm$ 20 percentage points assuming that the sensitivity was 80%. Specificity was estimated with a 95% CI $\pm$ 12 percentage points, assuming that the specificity was 80%.

The data was entered on to a spreadsheet (Excel, Microsoft corporation, US). To assess whether differences between infants who failed or succeeded extubation were statistically significant, the Mann–Whitney U test was used. Receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) calculated for TTdi, TTmus, respiratory muscle strength (Pimax, Pemax, Pdimax), respiratory drive (P0.1), the work of breathing (PTPdi) and the PIP and FiO<sub>2</sub> immediately before extubation. Analyses were undertaken using IBM SPSS statistical software (V.21). Comparison of the AUCs was undertaken using MedCalc statistical software (V.13.3.3) using the method of De Long et al [196]. We calculated the Youden' index to determine the optimal cut-offs for TTdi and TTmus. The Youden' index is defined by  $J = \text{Sensitivity} + \text{Specificity} - 1$ . The maximum Youden index is the optimal cut-off level.

## **7.3 Results**

### **7.3.1 Demographics**

Sixty infants (31 male) with a median gestational age of 35 (range 23–42) weeks and median birth weight of 2057 (range 464–4536) grams were studied at a median postnatal age of 5.5 (range 1–115) days. Thirty were born prematurely; their diagnoses at the time of the study were respiratory distress syndrome (n=20), bronchopulmonary dysplasia (n=8) and post surgery for necrotising enterocolitis (n=2). The diagnoses of the term-born infants were meconium aspiration (n=8), sepsis (n=8), post surgery (n=8) and transient tachypnea of the newborn (n=6).

Twelve infants (20%) failed extubation. Their median gestational age was 25 (range 23–39) weeks and median birth weight of 792 (464–2760) grams. Eleven of those who failed extubation had been born prematurely (median gestational age of 25 (range 23–29) weeks and median birth weight of 750 (range 464– 1056) grams). Eight infants were reintubated because of increased work of breathing, increasing oxygen requirement and development of a respiratory acidosis and four because of frequent apnoeas and bradycardias.

### **7.3.2 Outcomes**

The infants who failed extubation differed significantly from the rest of the cohort with regard to having a lower gestational age ( $p<0.001$ ), birth weight ( $p<0.001$ ),  $\text{FiO}_2$  ( $p<0.001$ ),  $\text{Pimax}$  ( $p=0.003$ ),  $\text{Pemax}$  ( $p=0.01$ ) and  $\text{Pdimax}$  ( $p=0.001$ ) and were of a greater postnatal age ( $p<0.001$ ) (table 7.1). The results for  $\text{Pimax/weight}$ ,  $\text{Pemax/weight}$  and  $\text{Pdimax}$  when related to birth weight did not differ significantly between the two groups (data not shown). The infants who failed extubation had a significantly higher  $\text{TTdi}$  ( $p<0.001$ ) and  $\text{TTmus}$  ( $p=0.003$ ) (table 7.1). The prematurely born infants who failed extubation were born at a lower gestational age ( $p=0.002$ ), of lower birth weight ( $p=0.007$ ), required a higher  $\text{FiO}_2$  prior to extubation ( $p=0.03$ ) and had higher  $\text{PTPdi}$  ( $p=0.006$ ),  $\text{TTdi}$  ( $p<0.001$ ) and  $\text{TTmus}$  ( $p=0.003$ ) (table 7.2).

	<b>Success</b>	<b>Failure</b>	<b>p Value</b>
N =	48	12	
Gestational age (weeks)	37 (24 – 42)	25 (23 – 39)	< 0.001
Birth weight (grams)	2684 (640 – 4536)	792 (464 – 2760)	< 0.001
Postnatal day of measure (days)	5 (1 – 115)	23 (2 – 102)	< 0.001
PIP before extubation (cm H <sub>2</sub> O)	16 (12 – 21)	16 (14 – 18)	0.73
F <sub>i</sub> O <sub>2</sub>	0.22 (0.21 – 0.60)	0.39 (0.22 – 0.48)	< 0.001
Pimax (cm H <sub>2</sub> O)	65 (16 – 125)	37 (9 – 88)	0.003
Respiratory drive (P <sub>0.1</sub> ) (cm H <sub>2</sub> O)	9.0 (1.5 – 32)	9.4 (1.7 – 18.7)	0.40
Pemax (cm H <sub>2</sub> O)	38 (6.56 – 121)	27.2 (15.0 – 42.7)	0.01
Pdimax (cm H <sub>2</sub> O)	84 (30 – 305)	48 (28 – 88)	0.001
PTPdi (cmH <sub>2</sub> O/s/min)	187 (20 - 534)	260 (102 - 561)	0.05
Tension time index of the diaphragm (TTdi)	0.04 (0.01 – 0.14)	0.15 (0.03 – 0.79)	< 0.001
Tension time index of respiratory muscles (TTmus)	0.08 (0.01 – 0.17)	0.17 (0.07 – 1.39)	0.003

**Table 7.1: Demographics and results according to extubation outcome.**  
**PIP, peak inflation pressure; PTPdi, transdiaphragmatic pressure-time product; Pimax, maximal respiratory muscle strength; Pemax, maximal expiratory muscle strength and Pdimax, the maximal transdiaphragmatic muscle strength. Data are expressed in median (range)**

	<b>Success</b>	<b>Failure</b>	<b>p Value</b>
N =	19	11	
Gestational age (weeks)	30 (24 – 36)	25 (23 – 29)	0.002
Birth weight (grams)	1320 (640 – 1980)	750 (464 – 1056)	0.007
Postnatal day of measure (days)	6 (1 – 115)	28 (2 – 102)	0.12
PIP before extubation (cm H <sub>2</sub> O)	16 (12 – 20)	16 (15 – 18)	0.16
F <sub>i</sub> O <sub>2</sub>	0.22 (0.21 – 0.60)	0.40 (0.22 – 0.48)	0.03
Pimax (cm H <sub>2</sub> O)	46 (15 – 79)	37 (9 – 88)	0.42
Respiratory drive (P <sub>0.1</sub> ) (cm H <sub>2</sub> O)	8.0 (2.8 – 17.7)	9.7 (1.7 – 18.7)	0.39
Pemax (cm H <sub>2</sub> O)	35 (6– 81)	27 (15 – 42)	0.17
Pdimax (cm H <sub>2</sub> O)	56.5 (30 – 305)	48.8 (28.4 – 88.7)	0.13
PTPdi (cmH <sub>2</sub> O/s/min)	132 (20 – 265)	233 (102 - 561)	0.006
Tension time index of the diaphragm (TTdi)	0.04 (0.02 – 0.14)	0.16 (0.03 – 0.79)	< 0.001
Tension time index of respiratory muscles (TTmus)	0.07 (0.03 – 0.17)	0.19 (0.08 – 1.39)	0.003

**Table 7.2: Demographics and results according to extubation outcome for the prematurely born infants. PIP, peak inflation pressure; PTPdi, transdiaphragmatic pressure-time product; Pimax, maximal respiratory muscle strength; Pemax, maximal expiratory muscle strength and Pdimax, the maximal transdiaphragmatic muscle strength. Data are expressed in median (range)**

The Area under the curve (AUCs) for TTdi and TTmus were 0.88 and 0.77, respectively, for all infants (table 7.3, figure 7.1) and 0.89 and 0.82, respectively, for prematurely born infants (table 7.4).

<b>Variable</b>	<b>Area under the curve (AUC's)</b>	<b>95% Confidence intervals</b>
Gestational age	0.88	0.78 to 0.99
Birth weight	0.89	0.79 to 0.98
PIP before extubation	0.47	0.75 to 0.96
F <sub>I</sub> O <sub>2</sub>	0.86	0.75 to 0.96
Pimax	0.77	0.64 to 0.90
Respiratory drive (P <sub>0.1</sub> )	0.58	0.43 to 0.65
Pemax	0.73	0.60 to 0.86
Pdimax	0.80	0.69 to 0.92
PTPdi	0.69	0.51 to 0.86
Tension time index of the diaphragm (TTdi)	0.88	0.75 to 1.00
Tension time index of respiratory muscles (TTmus)	0.77	0.60 to 0.91

**Table 7.3: Areas under the ROC curves.**

ROC, receiver operating characteristic; PIP, peak inflation pressure; PTPdi, transdiaphragmatic pressure-time product; Pimax, maximal respiratory muscle strength; Pemax, maximal expiratory muscle strength and Pdimax, the maximal transdiaphragmatic muscle strength.

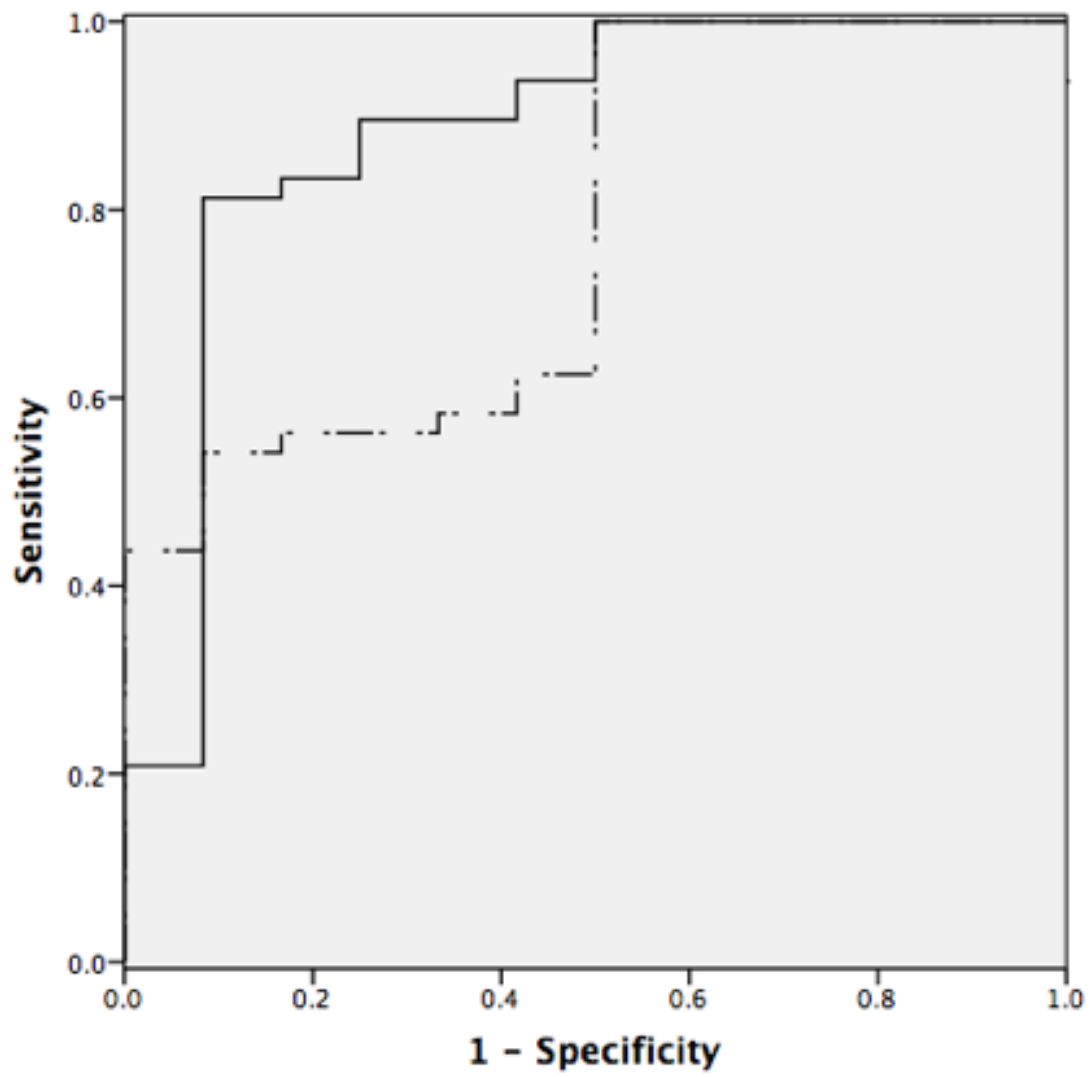


Figure 7.2: Receiver operator characteristic curves for TTdi and TTmus  
 \_\_\_\_\_ TTdi  
 ..... TTmus

<b>Variable</b>	<b>Area under the curve (AUC's)</b>	<b>95% Confidence intervals</b>
Gestational age	0.84	0.69 to 0.87
Birth weight	0.79	0.63 to 0.95
PIP before extubation	0.66	0.46 to 0.85
F <sub>i</sub> O <sub>2</sub>	0.73	0.54 to 0.91
Pimax	0.57	0.35 to 0.80
Respiratory drive (P <sub>0.1</sub> )	0.59	0.35 to 0.84
Pemax	0.66	0.45 to 0.85
Pdimax	0.68	0.48 to 0.88
PTPdi	0.79	0.63 to 0.96
Tension time index of the diaphragm (TTdi)	0.89	0.75 to 1.00
Tension time index of respiratory muscles (TTmus)	0.82	0.66 to 0.97

**Table 7.4: Areas under the ROC curves for prematurely born infants.**  
**ROC, receiver operating characteristic; PIP, peak inflation pressure; PTPdi, transdiaphragmatic pressure-time product; Pimax, maximal respiratory muscle strength; Pemax, maximal expiratory muscle strength and Pdimax, the maximal transdiaphragmatic muscle strength.**

Comparing the AUCs overall, TTdi and TTmus were significantly better predictors than the PIP before extubation ( $p \leq 0.001$ ,  $p = 0.04$ , respectively) (table 7.5). In the prematurely born infants, TTdi was a significantly better predictor than the PIP before extubation ( $p = 0.04$ ) and Pimax ( $p = 0.004$ ) and TTmus was a better predictor than the Pimax ( $p = 0.03$ ) (table 7.6).



	<b>TTdi p value</b>	<b>TTmus p value</b>
Gestational age	0.96	0.20
Birth weight	1.00	0.21
PIP before extubation	<b>&lt; 0.001*</b>	<b>0.04*</b>
F <sub>i</sub> O <sub>2</sub>	0.84	0.32
Pimax	0.20	0.98
PTPdi	<b>0.01^</b>	0.38

**Table 7.5: Statistical comparison of the AUCs for TTdi and TTmus with clinical data, PTPdi and Pimax. AUC, Area under the curve; PIP, peak inflation pressure; PTPdi, transdiaphragmatic pressure-time product; Pimax, maximal respiratory muscle strength, TTdi, tension-time index of the diaphragm; TTmus, tension-time index of the respiratory muscles..**

**\* For each comparison, the AUCs are greater for TTdi and TTmus than PIP**

**^ The AUC is greater for TTdi than PTPdi**

	<b>TTdi p value</b>	<b>TTmus p value</b>
Gestational age	0.54	0.87
Birth weight	0.31	0.83
PIP before extubation	<b>0.04*</b>	0.16
F <sub>i</sub> O <sub>2</sub>	0.11	0.39
Pimax	<b>0.004^</b>	<b>0.03^</b>
PTPdi	0.22	0.85

**Table 7.6: Statistical comparison of the AUCs for TTdi and TTmus with clinical data, PTPdi and Pimax in prematurely born infants. AUC, Area under the curve; PIP, peak inflation pressure; PTPdi, transdiaphragmatic pressure-time product; Pimax, maximal respiratory muscle strength, TTdi, tension-time index of the diaphragm; TTmus, tension-time index of the respiratory muscles..**

**\* The AUC is greater for TTdi than PIP**

**^ The AUCs are greater for TTdi and TTmus than Pimax**

Calculation of the Youden index demonstrated in the infants overall the optimal cut-off for TTdi was 0.08 (table 7.7) and for TTmus was 0.19 (table 7.8). Overall TTdi  $\geq 0.08$  had 83% sensitivity and 81% specificity and in the preterm infants a TTdi  $\geq 0.08$  had 90% sensitivity and 60% specificity in predicting extubation failure (table 7.9). Overall TTmus  $\geq 0.19$  had 50% sensitivity and 100% specificity and in the preterm infants 54% sensitivity and 100% specificity in predicting extubation failure (table 7.9).

<b>TTdi</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>Youden's index</b>
0.0113	1	0	0
0.0161	1	0.02	0.02
0.0170	1	0.04	0.04
0.0180	1	0.06	0.06
0.0202	1	0.08	0.08
0.0203	1	0.10	0.10
0.0203	1	0.10	0.10
0.0204	1	0.15	0.15
0.0244	1	0.17	0.17
0.0258	1	0.19	0.19
0.0302	1	0.21	0.21
0.0303	0.92	0.02	0.13
0.0313	0.92	0.23	0.15
0.0329	0.92	0.25	0.17
0.0354	0.92	0.27	0.19
0.0355	0.92	0.29	0.21
0.0380	0.92	0.31	0.23
0.0381	0.92	0.33	0.25
0.0385	0.92	0.35	0.27
0.0393	0.92	0.38	0.29

0.0393	0.92	0.38	0.29
0.0407	0.92	0.42	0.33
0.0416	0.92	0.44	0.35
0.0424	0.92	0.46	0.38
0.0424	0.92	0.46	0.38
0.0441	0.92	0.50	0.42
0.0454	0.92	0.52	0.44
0.0486	0.92	0.54	0.46
0.0500	0.92	0.56	0.48
0.0527	0.92	0.58	0.50
0.0550	0.92	0.60	0.52
0.0557	0.92	0.63	0.54
0.0563	0.92	0.65	0.56
0.0570	0.92	0.67	0.58
0.0572	0.92	0.69	0.60
0.0600	0.92	0.71	0.63
0.0736	0.92	0.73	0.65
0.0739	0.92	0.75	0.67
0.0750	0.92	0.77	0.69
0.0761	0.92	0.79	0.71
0.0775	0.92	0.81	0.73
0.1041	0.83	0.81	0.65
0.1059	0.83	0.83	0.67
0.1128	0.75	0.83	0.58
0.1128	0.75	0.83	0.58
0.1141	0.75	0.88	0.63
0.1145	0.75	0.90	0.65
0.1164	0.67	0.90	0.56
0.1207	0.58	0.90	0.48
0.1268	0.58	0.92	0.50
0.1330	0.58	0.94	0.52
0.1392	0.50	0.94	0.44

0.1442	0.50	0.96	0.46
0.1476	0.50	0.98	0.48
0.1638	0.50	1.00	0.50
0.1776	0.42	1.00	0.42
0.1791	0.33	1.00	0.33
0.1951	0.25	1.00	0.25
0.2041	0.17	1.00	0.17
0.7891	0.08	1.00	0.08

**Table 7.7: Sensitivity, Specificity and Youden's index for all possible cut-offs for observed values of TTdi.**

**\*Cut-off for TTdi giving maximum value of Youden's index.**

TTmus	Sensitivity	Specificity	Youden's index
0.0131	1	0	0
0.0300	1	0.02	0.02
0.0348	1	0.04	0.04
0.0399	1	0.06	0.06
0.0400	1	0.08	0.08
0.0411	1	0.10	0.10
0.0432	1	0.13	0.13
0.0461	1	0.15	0.15
0.0496	1	0.17	0.17
0.0508	1	0.19	0.19
0.0523	1	0.21	0.21
0.0560	1	0.23	0.23
0.0566	1	0.25	0.25
0.0678	1	0.27	0.27
0.0727	1	0.29	0.29
0.0730	1	0.31	0.31
0.0732	1	0.33	0.33
0.0732	1	0.33	0.33
0.0734	1	0.38	0.38

0.0749	1	0.40	0.40
0.0778	1	0.42	0.42
0.0780	1	0.44	0.44
0.0800	0.92	0.44	0.35
0.0800	0.92	0.46	0.38
0.0830	0.92	0.48	0.40
0.0921	0.92	0.50	0.42
0.0940	0.92	0.52	0.44
0.1150	0.92	0.54	0.46
0.1217	0.83	0.54	0.38
0.1239	0.83	0.56	0.40
0.1329	0.75	0.56	0.31
0.1365	0.67	0.56	0.23
0.1419	0.67	0.58	0.25
0.1429	0.58	0.58	0.17
0.1440	0.58	0.60	0.19
0.1461	0.58	0.63	0.21
0.1490	0.50	0.63	0.13
0.1500	0.50	0.65	0.15
0.1515	0.50	0.67	0.17
0.1516	0.50	0.69	0.19
0.1520	0.50	0.71	0.21
0.1550	0.50	0.73	0.23
0.1582	0.50	0.75	0.25
0.1582	0.50	0.75	0.25
0.1633	0.50	0.79	0.29
0.1635	0.50	0.81	0.31
0.1669	0.50	0.83	0.33
0.1685	0.50	0.85	0.35
0.1699	0.50	0.88	0.38
0.1700	0.50	0.90	0.40
0.1708	0.50	0.92	0.42

0.1746	0.50	0.94	0.44
0.1770	0.50	0.96	0.46
0.1783	0.50	0.98	0.48
0.1946*	0.50	1.00	0.50
0.2506	0.42	1.00	0.42
0.3158	0.33	1.00	0.33
0.3200	0.25	1.00	0.25
0.3600	0.17	1.00	0.17
1.3946	0.08	1.00	0.08

**Table 7.8: Sensitivity, Specificity and Youden's index for all possible cut-offs for observed values of TTmus.**

**\*Cut-off for TTmus giving maximum value of Youden's index.**

	<b>TTdi <math>\geq</math> 0.08</b>	<b>TTmus <math>\geq</math> 0.19</b>
<b>All Infants</b>		
Sensitivity (95% CI)	83% (10/12: 52% to 98%)	50% (6/12: 21% to 79%)
Specificity (95% CI)	81% (39/48: 67% to 91%)	100% (48/48: 93% to 100%)
<b>Preterm Infants</b>		
Sensitivity (95% CI)	90% (9/10: 56% to 100%)	54% (6/11: 23% to 83%)
Specificity (95% CI)	60% (12/20: 36% to 81%)	100% (19/19: 82% to 100%)

**Table 7.9: Sensitivity and specificity of TTdi and TTmus in predicting extubation failure**

#### **7.4. Discussion**

This study has demonstrated that the results of the TTdi and TTmus differed significantly according to extubation outcome in mechanically ventilated infants, born at term or prematurely. In a pilot study, our research group found that TTdi and TTmus performed similarly suggesting that TTmus might be used as a non-invasive alternative to TTdi [126]. In our study, however, which was three times larger, TTmus performed less well as indicated by a lower AUC (TTmus 0.77 vs TTdi 0.88). A possible explanation for the difference in the results of TTdi and TTmus is that there may be greater dysfunction related to prolonged ventilation of the diaphragm than that of the respiratory muscles. Prolonged mechanical ventilation can lead to 'ventilator-induced diaphragmatic dysfunction' [197], mechanical ventilation for only 18 hours has been shown to result in diaphragm atrophy and contractile dysfunction in animals and human beings [198]. This may result from increased diaphragmatic proteolysis, oxidative damage and reduced protein synthesis [199]. Furthermore, postmortem examinations carried out on 13 infants who had been mechanically ventilated for at least 12 days found significant reductions in diaphragm myofibre area and mass when compared with infants ventilated for 7 days or less prior to death [200].

The infants who failed extubation were also significantly more immature and of greater postnatal age. An older postnatal age has been previously reported [201] to be associated with extubation failure. In that study [201], however, infants studied were 14 days or less of postnatal age and all were born prematurely. In this study, we have included term and prematurely born

infants who were up to 4 months of age. The median PIPs did not differ significantly between infants who were and were not successfully extubated, which is consistent with the results of previous studies, highlighting information readily available to neonatologists may not always be helpful in deciding when to extubate an infant. Comparison of the AUCs highlighted that overall TTdi and TTmus performed significantly better than the PIP. Our results confirm that univariate indices such as Pimax, Pemax and Pdimax are not useful, as differences according to extubation outcome failed to reach statistical significance when the results were related to birth weight. There was, however, a significant difference in the PTPdi results and PTPdi is a composite assessment of readiness to extubate.

In 28 prematurely born infants, a TTdi  $\geq 0.12$  and TTmus  $\geq 0.10$  had 100% sensitivity and specificity in predicting extubation failure [199]. In our larger study, we could not replicate those results as TTdi  $\geq 0.12$  had 90% specificity (95% CI 77% to 96%) and 58% sensitivity (95% CI 77% to 96%) and TTmus  $\geq 0.10$  had 55% specificity (95% CI 27% to 84%) and 92% sensitivity (95% CI 61% to 99%). When we calculated Youden indexes to determine optimal cut-offs, the cut-off for TTmus was similar to that previously published (0.19 vs 0.18) [126,158]. The results for TTdi, however, were different (0.08 vs 0.15) [126,158]. The differences in the optimal cut-off to those previously published may reflect differences in the populations studied. Our population was more immature and their likely greater chest wall compliance, higher respiratory rates and more immature respiratory system could lead to a lower critical TTdi. A TTdi  $\geq 0.08$ , however, only had 81% specificity and 83% sensitivity



overall and 60% specificity and 95% sensitivity in the prematurely born infants in predicting extubation failure.

In conclusion, we have demonstrated that TTdi and TTmus results significantly differ according to extubation outcome in ventilated infants. Nevertheless, gestational age and birth weight performed similarly to TTdi and TTmus, as shown by the areas under the ROC curves. In addition, neither TTdi nor TTmus were 100% sensitive or specific in predicting extubation failure. Hence, neither can be recommended for use in routine clinical practice.

## **Chapter 8: Discussion**

## **8.1 Results from this thesis and current literature**

### **8.1.1 Resuscitation study**

This study demonstrated that higher inflation pressures, but not longer inflation times produced significantly higher expired tidal volumes. The effect of the higher inflation pressures was regardless of the inflation times. In the last few years, there have been differences regarding recommendations regarding the optimum inflation time. Whilst the European Resuscitation Council (ERC) guidelines suggest for the first few inflations to maintain the initial inflation pressure for two to three seconds [60], the American Heart Association states that “there is insufficient evidence to recommend an optimum inflation time” [78]. Indeed, our research group has demonstrated that despite maintenance of the inflation time for a median of 0.89 seconds the median inflation flow time was 0.11 seconds with no significant correlation with inflation flow time and the inflation time [59]. A Cochrane review [202] compared the outcomes of sustained ( $>$  one second duration) lung inflations compared to standard ( $\leq$  one second) inflations. Only two trials enrolling 352 infants between 25+0 to 28+6 weeks gestation and using a 15 second sustained lung inflation were identified. The results [202] showed that there were no differences in the rates of mortality during hospitalisation (RR 1.59, 95% CI 0.81 to 3.10), intubation in the first three days of life (RR 0.85, 95% CI 0.72 to 1.02) or chronic lung disease (RR 1.06, 95% CI 0.79 to 1.42) between infants who received sustained versus standard inflations. The rate of PDA (reported as need for pharmacological treatment) was increased in the sustained lung inflation group (RR 1.27, 95% CI 1.03 to 1.56) [202]. Therefore, at present, there is insufficient evidence from clinical trials to

determine the efficacy and safety of initial sustained lung inflation for newborn infants resuscitated with PPV. RCTs comparing PPV with and without sustained inflations at neonatal resuscitation are needed.

### **8.1.2 VTV versus PLV study in infants born at or near term**

This study has demonstrated no significant differences in the time to successful extubation in at or near term-born infants supported by VTV or PLV. In addition, there were no significant differences between the two groups in the results of physiological measurements performed prior to extubation. VTV, however, was associated with significantly fewer episodes of hypocarbia, despite the number of arterial blood gases being similar in the two groups. Reduction in episodes of hypocarbia in at or near term-born infants is an important outcome as studies have shown that hypocarbia is associated with PVL in prematurely born infants [183] and PVL had been reported in near term-born infants [184]. In addition, a poorer outcome has been documented in term-born infants with post-asphyxial hypoxic ischaemic encephalopathy exposed to severe hypocarbia [185,186]. There have been no further published studies exploring volume-targeted ventilation in infants born at or near term since this study was undertaken.

### **8.1.3 Proportional assist ventilation**

The randomised crossover study of PAV versus ACV demonstrated that PAV compared with ACV in prematurely born infants ventilated beyond the first

week after birth resulted in a reduced work of breathing and a lower OI. The lower OI is in keeping with the findings of Schulze and colleagues [109], that is despite a reduced mean airway pressure on PAV compared with ACV/SIMV, the inspired oxygen level and pulse oximetry readings were not significantly different on the two modes in very prematurely born infants (mean gestational age 25.6 weeks) with evolving chronic lung disease. In addition, the in-vitro assessment of the effects of PAV on resistive WOB study showed that resistive unloading was relatively ineffective and hence as currently delivered is unlikely to be of clinical benefit to infants with a high resistance load.

Following this study, our research group has undertaken a further study [192] to assess prematurely born infants with evolving bronchopulmonary dysplasia (BPD) in a randomised, crossover study comparing the results of four hour each of PAV and assist control. The results showed that during PAV compared to ACV, oxygenation was maintained at lower mean and peak inspiratory pressures. In addition, a significant reduction in the OI was reported on PAV [192]. In this study, similar to my study, only elastic unloading was used; resistive unloading was not employed because in vitro studies demonstrated that oscillations appeared in the airway pressure waveform when the resistive unloading was greater than 100 cm H<sub>2</sub>O/l/s [107,111].

#### 8.1.4 Tension-time index study

This study has demonstrated that TTdi and TTmus results significantly differed according to extubation outcome in ventilated infants. Nevertheless, gestational age and birth weight performed similarly to TTdi and TTmus, as shown by the areas under the ROC curves. In addition, neither TTdi nor TTmus were 100% sensitive or specific in predicting extubation failure.

Analysis of breathing patterns variability during spontaneous breathing under endotracheal tube continuous positive airway pressure (ETT-CPAP) has been proposed as a potential tool to predict extubation readiness in neonates [203]. In that study [203], the aim was to investigate if automated analysis of respiratory signals obtained from Respiratory Inductive Plethysmography (RIP) would reveal differences in respiratory breathing patterns between infants that were successfully extubated or not. The study included 56 infants with a birth weight less than 1250g enrolled at the time of their first extubation attempt. The signals were recorded during three minutes of spontaneous breathing while on ET-CPAP prior to extubation. The signals were then digitized, and analysed using an Automated Unsupervised Respiratory Event Analysis (AUREA) [203]. Extubation failure was defined as reintubation within 72 hours. The results showed significant differences between the groups in the variability of some respiratory parameters especially “respiratory frequency” and “ribcage movement artefact” [203]. Infants who failed extubation had a combination of low variability in the respiratory frequency ( $f_{\max}$ ) and high variability in the ribcage movement artifact metric ( $m^{rc}$ ). The optimal thresholds that best separated the two groups had a sensitivity of 82%

and specificity of 100% [203]. Although the study demonstrated that automated analysis of respiratory behaviour during a short ET-CPAP period may help in the prediction of extubation readiness in extremely preterm infants, the pathophysiological relevance of the metrics derived from AUREA is unknown [203] and the time spent on ET-CPAP of three minutes was empirical and short. Studies undertaking prospective validation of such tools are needed before they can be recommended for routine clinical practice.

Pre-extubation practices in neonates vary considerably; decisions are frequently physician dependent and not evidence based. The definition of extubation failure and the criteria for re-intubation are variable [125]. In a recent survey [204] undertaken to assess the pre-extubation practices in extremely preterm infants (less than 28 weeks gestation), 13 questions regarding weaning from mechanical ventilation, assessment of extubation readiness and post-extubation respiratory support were sent to clinical directors of level III NICUs in Australia, Canada, Ireland, New Zealand and USA. The study demonstrated that pre-extubation practices in extremely preterm infants varied considerably [204]. Extubation readiness was assessed based on multiple criteria, including ventilatory settings (98%), blood gases (92%) and the presence of clinical and haemodynamic stability (86%). Only 16% of units routinely used an SBT to determine readiness to extubate but up to 38% at least sometimes used it as part of their assessment. The SBT was of variable duration ranging from three minutes (25%) to more than 10 minutes (35%). Most of the centres were either neutral (55%) or disagreed (23%) with the idea that a SBT could help to predict extubation readiness

[204]. In addition, the definition of extubation failure was highly variable and well-defined criteria for reintubation were rarely used [204]. For example, in 88%, the decision to reintubate was based on the judgement of the clinician and there was a lack of clear time frame for the definition of extubation failure, although the majority proposing a period between 24 and 72 hours. The result of this study emphasizes that predicting the timing of extubation continues to be a challenge for clinicians. It is essential to identify objective criteria, which accurately predict successful extubation.



## **8.2 Strengths and weaknesses of the studies:**

### **8.2.1 Resuscitation study**

During all the resuscitations, a standard level of PEEP (4-5 cm H<sub>2</sub>O) was used. In this study a t-piece system was used to provide the PEEP as that system has been shown to provide more accurate and consistent PIP and PEEP compared to a self-inflating bag with a PEEP valve [205]. At inflation pressures less than 20 cm H<sub>2</sub>O, certain infants did not have measurable tidal volumes. Those infants had leaks within the range of the other infants. The results of this study again emphasize that despite intensive training in the stressful situation of labour suite resuscitation, UK recommendations are not always followed. Indeed, the majority of the operators did not maintain the inflation time for two to three seconds. This, however, gave the opportunity to compare different inflation times and pressures. The study does not report the results of a randomised trial, but a comparison of gestational age matched infants.

### **8.2.2 VTV versus PLV in infants born at or near term**

The same ventilator type was used in both arms of the study; performance differs according to type of ventilator delivering VTV with regard to airway pressure waveforms [206]. Comparison of VTV to PLV rather than a triggered mode was made, as no RCT has demonstrated better outcomes for triggered modes with regard to the duration of ventilation or need for reintubation in at or near term-born infants [189,190]. A limitation of this study may be perceived to be the heterogeneity of the population studied, yet a strength is

that they reflect the diagnoses of the currently ventilated infants born at or near term. In particular, in such a heterogeneous term-born population, we report a significant difference in an important outcome, the number of episodes of hypocarbia which influences long-term morbidity in such a population [185,186].

### **8.2.3 In vitro assessment of PAV**

Resistive unloading might be more effective if higher unloading levels could be used, but oscillations in the airway pressure waveforms were demonstrated in both in vitro [107,111] and in vivo [105] models at higher levels of unloading. Indeed, we noted airway pressure oscillations at an unloading level of 200 cm H<sub>2</sub>O/l/s and thus would not recommend higher levels of resistive unloading as currently delivered. The resistive WOB was not corrected for the tidal volume, as this would not be appropriate as resistive WOB is determined by flow rather than tidal volume and flow is a continuous variable. In our in vitro model, there was no leak in the system. Infants, however, are frequently ventilated by straight endotracheal tubes, and there is often a leak, which can be variable. Our results relate then to what will happen when there is minimal or no leak around the endotracheal tube.

### **8.4 Proportional assist ventilation**

This study demonstrated that PAV compared with ACV in prematurely born infants ventilated beyond the first week after birth resulted in a significantly reduced work of breathing and a lower OI. In this study, however, infants were

only studied for one hour each on PAV and ACV to see if infants tolerate the one hour period on PAV. Following this study, a further randomised crossover study [192] was undertaken by our research group wherein infants were studied for 4 hours each on PAV and ACV in random order and at the end of each 4-hour period, the oxygenation index (OI) was calculated. The median inspired oxygen concentration ( $p = 0.049$ ), mean airway pressure ( $p = 0.012$ ) and OI ( $p = 0.012$ ) were all lower on PAV [201].

### **8.2.5 Tension-time index study**

The study included term and prematurely born infants with a variety of pathologies and although it is not possible to comment on the usefulness of TTdi and TTmus for infants with a particular diagnosis, TTdi and TTmus overall and in the subgroup born prematurely differed significantly between those who did and did not fail extubation.

## **8.3 Future research**

Ventilatory strategies designed to improve patient-ventilator 'interaction' of which PAV and NAVA are examples, have continued to evolve. These modes aim to increase ventilatory support in response to increased work of breathing or effort. In infants with evolving or established BPD, the use of PAV needs further evaluation. The findings from the studies undertaken by our research group [190,192] and by Schulze et.al.[110] in premature infants has shown promising results but a randomised controlled trial with infants on PAV for a duration longer than 4 hours with long-term outcomes is needed to evaluate if

any benefit is appreciable in the long term before routine clinical use.

Neurally adjusted ventilatory assist (NAVA) is a novel mode of ventilation that has been demonstrated to improve infant-ventilator interaction, compared to the conventional modes in retrospective and short-term clinical studies [207-212]. NAVA utilises the diaphragmatic electrical activity (EAdi) to trigger both the initiation and the termination of inflation. This therefore allows a bypass of inherent trigger delays in a pneumatic circuit. Additionally, the pressure support delivered is coupled with the magnitude of the EAdi. The EAdi is measured using a nasogastric EMG catheter. In the neonatal population this mode has been compared in a number of crossover trials to date to modes such as PSV and ACV [207-210]. Data from these studies suggest an improved patient ventilator synchrony [207,209], lower peak pressures [209] with a lower work of breathing [208]. Some authors believe that NAVA is more suitable for a wider range of infants than PAV including the most premature infants, due to more accurate triggering and delivery of ventilator support regardless of leak around the endotracheal tube [211]. Studies evaluating NAVA with other modes of ventilation have been small. Since VTV has been shown to improve both short term and long term outcomes in prematurely born infants, randomized trials comparing NAVA with volume targeted ventilation (VTV) in newborns to see if NAVA is superior to VTV would be useful. As most previous studies and trials were small and did not include long-term patient oriented outcomes, randomized controlled trials are needed to determine whether NAVA is effective in avoiding the need for intubation, decreasing the duration of ventilation, reducing the incidence of BPD and decreasing length of stay, rate of pneumothorax and IVH.

## 8.4 Conclusions

Higher inflation pressures, but not longer inflation times produced significantly higher expired tidal volumes. Although there were no significant differences in the time to successful extubation in at or near term-born infants supported by VTV or PLV, VTV was associated with significantly fewer episodes of hypocarbia. PAV compared with ACV in prematurely born infants ventilated beyond the first week after birth resulted in a reduced work of breathing and a lower OI. In an in-vitro model, during PAV the resistive unloading was relatively ineffective and hence as currently delivered is unlikely to be of clinical benefit to infants with a high resistance load. Overall TTdi  $\geq 0.08$  had 83% sensitivity and 81% specificity in predicting extubation failure. Overall TTmus  $\geq 0.19$  had 50% sensitivity and 100% specificity in predicting extubation failure.

## 8.5 References

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